UNIVERSITY/INDUSTRY COOPERATION IN BIOTECHNOLOGY

HEARINGS

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

AND THE

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

NINETY-SEVENTH CONGRESS

SECOND SESSION

JUNE 16, 17, 1982

[No. 138]

Printed for use of the
Committee on Science and Technology

U.S. GOVERNMENT PRINTING OFFICE
99-177 O WASHINGTON : 1982

H701-14

COMMITTEE ON SCIENCE AND TECHNOLOGY

DON FUQUA, Florida, *Chairman*

ROBERT A. ROE, New Jersey
GEORGE E. BROWN, JR., California
JAMES H. SCHEUER, New York
RICHARD L. OTTINGER, New York
TOM HARKIN, Iowa
MARILYN LLOYD BOUQUARD, Tennessee
JAMES J. BLANCHARD, Michigan
TIMOTHY E. WIRTH, Colorado
DOUG WALGREN, Pennsylvania
RONNIE G. FLIPPO, Alabama
DAN GLICKMAN, Kansas
ALBERT GORE, JR., Tennessee
ROBERT A. YOUNG, Missouri
RICHARD C. WHITE, Texas
HAROLD L. VOLKMER, Missouri
HOWARD WOLPE, Michigan
BILL NELSON, Florida
STANLEY N. LUNDINE, New York
ALLEN E. ERTEL, Pennsylvania
BOB SHAMANSKY, Ohio
RALPH M. HALL, Texas
DAVE McCURDY, Oklahoma
MERVYN M. DYMALLY, California
LARRY WINN, JR., Kansas
BARRY M. GOLDWATER, JR., California
HAMILTON FISH, JR., New York
MANUEL LUJAN, New Mexico
HAROLD C. HOLLENBECK, New Jersey
ROBERT S. WALKER, Pennsylvania
EDWIN B. FORSYTHE, New Jersey
WILLIAM CARNEY, New York
MARGARET M. HECKLER, Massachusetts
F. JAMES SENSENBRENNER, JR., Wisconsin
VIN WEBER, Minnesota
JUDD GREGG, New Hampshire
RAYMOND J. McGRATH, New York
JOE SKEEN, New Mexico
CLAUDINE SCHNEIDER, Rhode Island
JIM DUNN, Michigan
BILL LOWERY, California

HAROLD P. HANSON, *Executive Director*
ROBERT C. KETCHAM, *General Counsel*
REGINA A. DAVIS, *Administrator*
GERALD E. JENKS, *Minority Staff Director*

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

ALBERT GORE, JR., Tennessee, *Chairman*

BOB SHAMANSKY, Ohio
HAROLD L. VOLKMER, Missouri
ROBERT S. WALKER, Pennsylvania
MANUEL LUJAN, JR., New Mexico

ROBERT B. NICHOLAS, *Chief Counsel/Staff Director*
JAMES E. JENSEN, *Investigator*
DAVID D. CLEMENT, *Minority Counsel*

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

DOUG WALGREN, Pennsylvania, *Chairman*

GEORGE E. BROWN, JR., California
BOB SHAMANSKY, Ohio
MERVYN M. DYMALLY, California
STANLEY N. LUNDINE, New York
ALLEN E. ERTEL, Pennsylvania
RALPH M. HALL, Texas
DAVE McCURDY, Oklahoma
MARGARET M. HECKLER, Massachusetts
VIN WEBER, Minnesota
JUDD GREGG, New Hampshire
JOE SKEEN, New Mexico
EDWIN B. FORSYTHE, New Jersey

CONTENTS

WITNESSES

June 16, 1982:

Page

Dr. David M. Kipnis, Head of the Department of Internal Medicine at Washington University, St. Louis, Mo., and Dr. Howard A. Schneiderman, Senior Vice President, Research and Development, Monsanto Co., St. Louis, Mo. 8

Albert H. Meyerhoff, Senior Attorney, Natural Resources Defense Council, San Francisco, Calif.; and Dr. Charles Hess, Dean, College of Agricultural and Environmental Sciences, University of California at Davis. 49

Dr. Charles Muscoplat, Vice President for Medical Products, Molecular Enetics, Golden Valley, and James William Chaney, Vice President, Agrigenetics, Denver, Colo., accompanied by R. N. Dryan, president, Agrigenetics 89

June 17, 1982:

Dr. Robert Rosenzweig, Vice President for Public Affairs, Stanford University; Dr. Robert M. Bock, Dean of Graduate School, University of Wisconsin; and Dr. Roderic B. Park, Vice Chancellor, University of California at Berkeley 105

Dr. William F. Raub, Associate Director for Extramural Research and Training, National Institutes of Health, Public Health Service, Department of Health and Human Services; and Dr. Donald Senich, Director, Division of Industrial Science and Technological Innovation, National Science Foundation 131

APPENDIX

Additional Material for the Record

1. Letter to Congressman Gore from Dr. David Kipnis and Dr. Howard Schneiderman 155
2. Letter to Congressman Gore from Edward MacCordy 157
3. Letter to Congressman Gore from Donald Kennedy 159
4. Letter to Congressman Gore from Albert H. Meyerhoff 160
5. Letter to Mr. Albert Meyerhoff from Patricia L. Devaney 162
6. Office memorandum concerning outside consulting activities from the vice provost and dean of graduate studies, Stanford University 163
7. Stanford University excerpt from the minutes of the academic council, October 15, 1981 164
8. Stanford University excerpt from the minutes of the academic council, November 12, 1981 168
9. Articles, "The Gene Merchants" and "Strained Relations" from California magazine, September 1982 171
10. Letter to Dean Charles Hess from Prof. Paul K. Stumpf 179
11. "Research," the publication of the University of Wisconsin-Madison university-industry research program 180
12. University of Wisconsin-Madison publication on the occasion of the 50th anniversary of the Wisconsin Alumni Research Foundation [WARF] 181
13. Article, "The Unpredictable Payoffs of Basic Research" 240
14. Statement by Arthur Hull Hayes, Commissioner, Food and Drug Administration, on the release of a new vaccine for Hepatitis B 256
15. Minutes of NIH site visit to Massachusetts General Hospital 261

UNIVERSITY/INDUSTRY COOPERATION IN BIOTECHNOLOGY

WEDNESDAY, JUNE 16, 1982

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY,
Washington, D.C.

The subcommittees met, pursuant to call, at 9:30 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the Subcommittee on Investigations and Oversight) presiding.

Mr. GORE. The subcommittees will come to order.

I would like to welcome all of our witnesses and guests to the second joint hearing on the commercialization of biomedical research, with a special emphasis on university/industry arrangements in this area.

We initially convened these hearings 1 year ago to examine the important public issues involved when massive amounts of money are provided to universities to exploit research and commercial potential in the field of biotechnology. At the time of our first hearing, there were few major agreements, the largest being the $50 million agreement between Massachusetts General Hospital and Hoechst, a German chemical company.

We return at a time when the number of such agreements is mushrooming and the dollar amount is now in excess of $200 million. We return also at a time when some of the flash of this new, multimillion-dollar technology has been dulled by the painful realities of a sluggish economy.

We return with a renewed sense of urgency that our innovative potential as a country and our technological competitiveness in world markets is lagging. And we return with a sense of hope and continued expectation as some of the promises of biotechnology have borne fruit and others continue to be developed.

Finally, we return with a continuing concern that our universities, the source and foundation of these technologies, may be permanently altered by the increasing number of commercial agreements that they are developing. We do not view such agreements as bad, per se, but rather as a development that needs to be examined in detail and dealt with carefully lest we adversely affect one of America's greatest strengths.

In the year that has elapsed since our hearings last June, numerous university-industry ties have been announced. Some, as we will

hear today, have resulted in difficult problems for the university; others do not seem to involve these pitfalls. We are encouraged by several of the recent efforts being made in the academic community to discuss the issues of concern. We will hear about some of these efforts during the course of our hearings. It is our expectation that through these hearings we can learn more about how to avoid the pitfalls and maximize the benefits for all.

As part of our efforts to obtain a better appreciation of the issues, the Science and Technology Committee sent a questionnaire to approximately 50 universities. The questionnaire sought data to assess one, the extent of industry arrangements in biotechnology areas; two, the nature of the patent and licensing provisions in those agreements, and three, the institutional provisions for dealing with commingling of industry-government funds and potential conflict of interest involving faculty members.

While the number of institutions responding was very good, some institutions were less than forthcoming with information on their specific contractual agreements. In all, the questionnaire tells us that the commercialization of biotechnology is still in a period of evolution with each institution trying to find its own particular path to successful university-industry interaction. The subcommittee plans site visits to develop the additional necessary data.

The trend of industry financing of university research is obviously growing in part because of the financial realities which universities have to face, and in part because industry can benefit tremendously by partaking of the wealth of basic scientific expertise and innovation provided by the university researchers. Some interaction is necessary as well, to promote technology transfer in both directions.

I have been critical of some university-industry agreements in biomedical research. The concerns I raised 1 year ago are the ones that I reiterate today. The moral and ethical implications of gene therapy and manipulation, ownership of infectious disease organisms and antibodies, and intellectual property rights are waiting to be addressed. Issues that the universities face—conflicts of interest, allocation of resources, teaching of graduate students, shifting research priorities, publication of research results, and the struggle to remain economically solvent—are of an immediate nature and require careful scrutiny.

The need to have an objective scientific group to address these ethical and institutional issues for the public interest is clear and is strengthened by similar needs of the Federal Government. We are a nation that is increasingly dependent upon science and technology. The regulations we formulate which impact upon our health, economy, environment, and defense need to be firmly based on scientific data. We turn to our scientists to interpret that data in an objective manner.

In a similar way, we rely upon a base of scientists to determine, by peer review, into what channels Government research money should be funneled. It is critical that we maintain a group of scientists who can speak freely to these issues and whose perspectives, to the public eye, are not cast into doubt by their associations with industry.

The purpose of these hearings for the next 2 days is threefold: First, to discuss the current extent of university-industry arrangements in biotechnology and assess both the positive and negative aspects of such agreements; second, to ascertain the Federal role in ensuring the proper return of the taxpayers investment, and third, to discuss how these arrangements are perceived from both the industry and university viewpoint.

Of particular interest are questions which will afford us some insights into how the whole phenomenon is evolving:

First, what can be learned from current university—industry agreements in biotechnology?

Second, how are universities coping or planning to cope with difficult institutional and ethical questions?

Third, what are industries' needs in biotechnology and how do ties with universities satisfy these needs?

Fourth, what role should the Federal Government play in maintaining a balance between the need for technological innovation and the need to safeguard the university as basic science research center?

In the next 2 days, we will be hearing from experts from three sectors involved with these agreements. Today we will learn about two specific agreements in the biotechnology area: The first between the University of California at Davis, Calgene, and Allied Chemical and the second between Washington University in St. Louis and the Monsanto Co. The perspective of the smaller biotechnology firms will follow.

Tomorrow we will hear testimony from the universities and a representative of two scientific societies, followed by the perspective of the two major Government granting institutions for scientific research, the National Institutes of Health, and the National Science Foundation.

In closing, let me say that I am pleased to welcome our witnesses today to hearings on a topic of importance to us all. I would also like to read a thought that Alfred North Whitehead—(not the MIT Whitehead)—expressed nearly 60 years ago. It captures the nature of the dilemmas we will address today:

> There are two principles inherent in the very nature of things, recurring in some particular embodiments whatever field we explore—the spirit of change and the spirit of conservatism. There can be nothing real without both. Mere change without conservatism is a passage from nothing to nothing. * * * Mere conservatism without change cannot conserve. * * * The character of existent reality is composed of organisms enduring through the flux of things.

I would like unanimous consent to include at this point in the record a statement from Chairman Doug Walgren, who is co-chairing these hearings.

[Opening Statement of Mr. Walgren follows:]

OPENING STATEMENT
HONORABLE DOUG WALGREN
HEARING ON
UNIVERSITY/INDUSTRY COOPERATION
IN BIOTECHNOLOGY

JUNE 16, 1982

On behalf of the Subcommittee on Science, Research and Technology I would like to welcome you all to this hearing.

The subject of university-industry relationships has been widely discussed: in the scientific press, the popular press, on university campuses and in corporate boardrooms.

I don't believe that anyone would disagree that there is an "innovation problem" in the U.S. today. This problem is reflected in declining competitiveness in world markets and the increasing domination of foreign manufactured goods in U.S. markets.

Certainly, improved relationships between universities and industries could help to foster innovation and increase productivity in the U.S. These relationships have taken a number of different forms: outright unrestricted grants, contracts for specific projects, industrial monies administered through third-party foundations or state-run biotechnology centers. We shall hear about two of these arrangements today.

THE IDEA OF INDUSTRIES FUNDING UNIVERSITY RESEARCH IS NOT NEW. BENEFICIAL LIAISONS BETWEEN THE TWO HAVE EXISTED IN PHYSICS, CHEMISTRY, COMPUTER SCIENCE AND CERTAIN ENGINEERING SCIENCES FOR DECADES. IN FACT, UNIVERSITY RESEARCH PRIOR TO 1950 WAS FUNDED BY INDUSTRY TO A SIGNIFICANT DEGREE. SINCE THAT TIME THE FEDERAL GOVERNMENT HAS LARGELY SUPPORTED CAMPUS-BASED RESEARCH WITH ONLY A SMALL, YET STABLE, PROPORTION CONTINUING TO BE FUNDED BY INDUSTRY.

HOWEVER, IN RECENT YEARS WE HAVE BEEN FACED WITH A DILEMMA. MANY OF THE DEVELOPMENTS IN MOLECULAR BIOLOGY, GENETICS AND CELL BIOLOGY CAN BE COMMERCIALIZED ALMOST IMMEDIATELY AND MANY OF THE FACULTY DOING THIS RESEARCH HAVE BECOME PERSONALLY INVOLVED IN THE COMPANIES COMMERCIALIZING THE RESEARCH. THIS HAS BLURRED THE TRADITIONAL DISTINCTION BETWEEN "BASIC" RESEARCH USUALLY DONE IN UNIVERSITIES AND "APPLIED" RESEARCH AND DEVELOPMENT USUALLY DONE IN AN INDUSTRIAL LABORATORY. THIS RESEARCH IN THE BIOTECHNOLOGIES HAS THE POTENTIAL TO GENERATE FUNDS FOR UNIVERSITIES, MANY OF WHICH ARE ACTIVELY SEEKING ALTERNATIVE FUNDING SOURCES. YET, THE VERY PROCESS OF DEVELOPING THIS POTENTIAL MAY CHANGE THE FUNDAMENTAL MISSION OF UNIVERSITIES, THAT IS, EDUCATION AND RESEARCH IN AN ATMOSPHERE OF FREEDOM OF THOUGHT AND FREE EXCHANGE OF IDEAS.

THIS DILEMMA HAS RAISED MANY QUESTIONS AND ANSWERED FEW.

FOR EXAMPLE, CAN THE UNIVERSITIES SUCCESSFULLY PRESERVE THE FREE EXCHANGE OF IDEAS BETWEEN STUDENTS AND FACULTY WHILE MEETING THE OBLIGATION OF INDUSTRIAL ARRANGEMENTS.

SHOULD CORPORATE SPONSORSHIP BE SUBJECT TO PEER REVIEW?

HOW SHOULD PATENT RIGHTS BE ASSIGNED AMONG THE UNIVERSITY, THE SCIENTIST AND THE INDUSTRY IN A JOINT VENTURE?

ARE GRADUATE STUDENTS AND POST-DOCTORAL TRAINEES BEING ADVERSELY AFFECTED OR ARE THEY BENEFITTING FROM ADDITIONAL INDUSTRIAL FUNDS FOR FELLOWSHIPS AND RESEARCH SUPPORT?

SHOULD THE STATE OR FEDERAL GOVERNMENTS PLAY A ROLE IN ENCOURAGING THESE RELATIONSHIPS, AND IF SO, WHAT SHOULD IT BE?

WE WILL BE HEARING FROM WITNESSES REPRESENTING ACADEMIA, INDUSTRY, THE FEDERAL GRANTING AGENCIES AND THE MAJOR SCIENTIFIC SOCIETIES. WE WISH TO PROVIDE A FORUM TO EXPLORE THESE DIFFICULT AND IMPORTANT ISSUES.

WE HOPE THAT THESE HEARINGS WILL PROVIDE INSIGHTS ON HOW CONGRESS CAN WORK TOGETHER WITH UNIVERSITIES AND INDUSTRIES TO RESOLVE THE ISSUES IN A MUTUALLY AGREEABLE AND BENEFICIAL WAY.

I AM LOOKING FORWARD TO THE TESTIMONY. I WOULD LIKE PARTICULARLY TO RECOGNIZE THE ROLE OF MY COLLEAGUE, CHAIRMAN GORE, IN FOCUSING THE ATTENTION OF OUR MEMBERS ON THIS IMPORTANT AND TIMELY SUBJECT.

Mr. GORE. Now I would like to recognize the ranking minority member of the Investigations Subcommittee, Mr. Walker.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. Chairman, our hearings today are a continuation of hearings we held last year to examine the contract between Massachusetts General Hospital and Hoechst, a German chemical multinational conglomerate.

Congressional concerns in this area have not abated in the past year. In fact, they have grown larger. We are concerned about the possibility that these university-industry relationships may eventually lead to serious problems with conflicts of interest.

Over the years the Congress, and particularly the Committee on Science and Technology, has strongly defended and protected our Nation's science base within the academic community. Congress has decided that it was certainly the proper role of Government to annually fund basic research through the Government so that scientific innovation would continue to flourish in this country.

But after decades of following that course, we are now starting to see that new relationships may be developing. A number of large corporations are making heavy investments in college and university centers of research. While the investments should be applauded, we cannot help but wonder what strings, real or imagined, may go with those investments?

We must be concerned over the possibility that important new research may be abandoned in a laboratory simply because it appears that it may not be of importance to a corporate benefactor.

We must be concerned that the interrelationships between laboratory directors and their corporate sponsors may lead to an improper or unethical concentration on work in behalf of the sponsor. And, as the keepers of the public purse, we must also be concerned that the tremendous scientific base developed within the United States over the years at the expense of the taxpayer is not now going to be put to the exclusive use of the highest bidder.

None of these concerns seem to be realized at this time, and we hope that none of them ever will be realized. But we have a heavy duty under the Constitution to safeguard the public purse and to oversee the activities funded by our Government. It seems obvious to us that the potential impacts of these new agreements may, and I stress may, affect various academic traditions concerning open and free exchange of information, cooperation among faculty, training of graduate students and, most importantly, free and open peer review of research results.

Finally, we must also look into the question of exactly what safeguards may become necessary to protect the people's interests in their investments in biomedical research.

Mr. Chairman, as an educator I cannot help but be aware that this sort of inquiry may be the cause of some concern in the academic community. But I want to assure those who may have trouble understanding why a committee of the Congress should be interested in this area that we can, and must, have a proper role to play as the academic community moves into an era of new relationships with nongovernmental sponsorship of research. This committee has always been in favor of basic research, and we continue that support today. But our concern is that the science base that

has been developed over the years must continue to be available to all, and it must be used for the public benefit.

As long as there are proper safeguards to protect the public, there should be no problems in these new agreements. Still we must be assured that those safeguards are understood and in place.

Thank you very much.

Mr. GORE. I would like to call our first panel of witnesses. I see they have already joined us. We are delighted to welcome Dr. Howard Schneiderman, senior vice president of Research and Development at Monsanto Co., and Dr. David Kipnis, Adolphus Busch professor of medicine, and chairman of the Department of Internal Medicine at Washington University in St. Louis.

It is very timely we have the opportunity to discuss with you gentlemen the brand new agreement that was announced so recently, that deals with some of the same issues that this subcommittee—that these subcommittees have been exploring.

Without further ado, let me tell you without objection the entire text of your prepared statements will be included in the record, and invite you to proceed.

STATEMENTS OF DR. DAVID M. KIPNIS, HEAD OF THE DEPARTMENT OF INTERNAL MEDICINE, WASHINGTON UNIVERSITY, ST. LOUIS, MO., AND DR. HOWARD A. SCHNEIDERMAN, SENIOR VICE PRESIDENT, RESEARCH AND DEVELOPMENT, MONSANTO CO., ST. LOUIS, MO.

Dr. KIPNIS. I think I will start our presentation.

On behalf of my colleagues, I would like to thank the subcommittee for the opportunity of presenting testimony on many issues that we too are concerned with in the academic community.

What I would like to do is to summarize the written testimony that we submitted to the committee, deal with the reasons why we pursued an industrial relationship, why Monsanto was the company with which we became involved, and deal with certain unique aspects we feel of the contractual agreement.

Our goals were to enhance the scientific resources available to our faculties at the university. This reflects the fact that our academic faculties have been experiencing increasing concern for the future of their basic and clinical research in view of governmental policies during the past decade or so, and also at a time when many of us feel that the scientific revolution that has occurred in the biological sciences opens up extraordinary opportunities to deliver to the public new products and technologies dealing with a wide variety of diseases for which at the present time we have no definitive therapy.

I think it also important to point out that over the last two to three decades there has been an increasing social concern by our faculties reflecting the fact that the students of college campuses of the 1960's are now the assistant professors of our faculties today.

Furthermore, at medical centers we have been extraordinarily deeply involved in health care delivery to certain segments of our population, particularly during the past two decades.

In addition, academic faculties live in regions, and their capacity to compete for the finest brains for their universities frequently re-

flect the resources that region can bring to bear on the universities' health and vitality.

In this sense we felt we should be an active participant in attracting and establishing arrangements which would increase the technology skills of our region at the national level.

Now, the reason we involved ourselves with Monsanto reflects, again, certain unique aspects of our location in St. Louis.

First, we are geographically approximate.

Second, the founding families of Monsanto have been intimately involved with the university for many, many years.

Third, many of our academic faculties have had individual relationships for many years with scientists at Monsanto.

Fourth, Monsanto has made evident over the last 5 or 10 years that they were interested in expanding their involvement in the biological and health care areas.

And lastly, about 2½ or 2 years ago, when Dr. Howard Schneiderman came to Monsanto as the senior vice president in charge of research, it became very evident to us that a scientist of international repute and accomplishment was now joining the company and would be very attractive for us to interrelate with.

Also, it would be important to point out that Dr. Schneiderman approached our senior administrators about 2½ years ago to develop contacts to explore the evolution of a new collaborative venture.

During the last 2½ years, significant elements of our senior faculty, initially 6 and expanded ultimately to the range of 15 or 20, engaged in very in-depth discussions about a wide variety of the issues that this committee has been concerned within the past 2 to 3 years, as to how universities should relate with high technology industry.

Our interactions actually involved a retreat of over 3 days in which some 15 to 20 accomplished senior scientists at the university presented indepth science presentations to corresponding scientists, managers, and senior officers of the company, and where extensive and candid views about institutional goals, institutional values, were exchanged.

Subsequently, I served as spokesman for the academic faculty involved, and we spent most of our time focusing on the nature of the relationship.

Once that was clearly defined, we then spent time in defining an area of science, not a product and not a technology, but an area of science where the university had extraordinary strengths. An area where the university's senior faculty felt there were great exciting opportunities for new basic and clinically applicable kinds of research, and then we interacted with Monsanto in that context.

And finally the agreement was signed.

I would like to focus on several aspects of the agreement that we feel address many of the issues that have been raised by this committee and which we believe offer guidelines to other institutions involved with or seeking similar kinds of collaborative efforts.

The first aspect is that our senior faculty thought that a relationship of this nature should be institutional.

I also want to point out a critical factor to be recognized in these industrial-academic relationships, and that is the issue of scale. If industrial support of university biomedical research which exists

today were to be trebled, it would still only constitute about 10 percent of the total research budgets of universities supported currently by the National Institutes of Health and the National Science Foundation.

In this context, it seems to us highly unlikely that carefully thought-out agreements which will distort the direction of its research is the primary goal of the university.

We felt at least at our institution it would be wise to have institutional relationships rather than having relationships between companies and individual faculty members. We wanted to avoid issues of divisiveness. We wanted to avoid issues of having one or two or a few professors very well funded in what might be thought of by some as a noncompetitive stance in relationship to large segments of the community that are constantly competing for limited research funds.

This was rapidly agreed to by our faculties and Monsanto.

The next, in order to avoid distortions and maintain quality, was to introduce the peer review system. I would point out that for 30 years our academic institutions have been learning in an evolutionary manner how to protect themselves against governmental intrusion. Government support is not always benign. It also has the potential of intruding on the governance of universities and it certainly influences the direction of research.

One of the major protections has been the introduction of the peer review system and, therefore we chose to build into this collaborative effort, this partnership we have entered into, has been both an internal peer review system as well as an external peer review system.

Internal peer review is accomplished by an advisory committee with science representatives from both the university as well as the company, and external peer review is done at frequent intervals, initially in 3 years, subsequently every 2 years thereafter by nationally and internationally recognized scientists, independent of either the company or the university, who report directly to the chancellor of the university, the chairman of the company, and to the advisory committee.

We also wanted to have funds in an area which would allow competition by the faculty and the research approved on the basis of its scientific merit and its relevance to the area of interest. And for this reason, nowhere in our contract do we spell out specific research projects. Rather, again from our lessons in the Government, we intend to circulate the faculty with ARFP, a request for programs, in which the areas are described in which faculty will submit research proposals to be reviewed by the committee.

We also wanted the expenditures and level of expenditures to represent a significant sum of funds which would enhance our research opportunities for new ventures, but not to represent that degree of funding which could potentially distort the directions of our institution.

I would point out to you that last year Washington University School of Medicine received in excess of $50 million from the NIH for support of its biomedical research program and at least another $5 million from other private health sources.

In the first year of this grants operation, there will be $3 million, eventually building up to the level of $6½ to $7 million. Therefore, it will constitute, at most, somewhere of the order of 5 to 6 percent of our total research budget. That was done by design of the faculties to make certain that it was not, in essence, a situation where the perception either of the public or of its own academic faculties would be that the company was buying a university or that the university was the only university with which a company would operate.

We feel quite free to relate with any other corporate institution, and we certainly think that Monsanto feels free to relate with any other research institute or university.

The purpose of the funds is to engage in new and expanded research. We do not perceive it as a substitute for Government support of research. We hope that Government agencies would also recognize this. Quite frankly, academic faculties have anxiety about the possibility that these kinds of agreements will impair the competitiveness of our faculties for traditional sources of governmental funds.

We also guaranteed within the contract that all of our scientists will have the freedom to publish all of their results. We merely ask that our scientists submit to the advisory committee and to the corporation for review for potential patentability their initial drafts of papers, at which time there will be 3 days to review it.

We have also done something else which we feel important, but it is in the context of Washington University. At our university, all of our full-time people are strictly on salaries. We do not have plans where there is a tie-in with the volume of practice and the income our faculties derive from this practice. All clinical practice money goes to the university to support its research and training programs. We felt that any royalties which might be derived from efforts funded by a corporation would also be accordingly allocated.

Therefore, all scientists at our institution involved in this agreement signed over the royalties to the institution under the terms that approximately 20 percent will go to the medical school for support of its general research and training programs, 40 percent to the cognizant department in which the laboratory is located, and the reward to the scientist, in terms of 40 percent of the funds, to support his or her research and training program.

We felt that many of our academic faculty entered academic life for the excitement and the privileges and the perks of academic life, not for individual return, and therefore the returns from this contract are also on the same basis.

Now, it is our personal feeling that we have attempted to address many of the concerns that we have had and that have been expressed at previous hearings of this committee.

We think that our agreement represents a significant step in the evolution of industrial-academic collaboration. And although the specifics of the agreement suit the unique traditional geographic and scientific characteristics of Monsanto and Washington University, we feel that some of the institutional values and procedures which we used in evolving this kind of agreement may be useful to other institutions seeking to develop similar collaborative programs with industry. Thank you very much.

[The prepared statement of Dr. Kipnis follows:]

TESTIMONY BY DAVID M. KIPNIS, M.D., DEPARTMENT OF INTERNAL MEDICINE, WASHINGTON UNIVERSITY, ST. LOUIS, MO.

Mr. Chairman, Members of the Committee and Subcommittee

I am David M. Kipnis*, M.D., Busch Professor and head of the Department of Internal Medicine at Washington University in St. Louis. I have prepared a statement for these hearings, but as you know, Mr. Chairman, this preparation has been made on very short notice. I consider these hearings very important and I am pleased to have this opportunity to testify before you today to discuss the recently consummated agreement between the Monsanto Company and Washington University. We have provided for the Committee the news release and background statement describing this relationship which was announced just two weeks ago on June 3. We believe that this agreement incorporates many unique and special provisions that go a long way in addressing many of the concerns that have been raised both publicly and privately over what appears to be a new era in biomedical research signified by an increasing number of academic-industrial arrangements to support basic and applied research.

There is a crucial point that we believe should be established in everyone's minds as we consider these new relationships. Industry support should not be considered as a replacement for federal support of basic and clinical biomedical research. Simply as a matter of scale, Mr. Chairman, continued federal support is essential. If the current level of industrial support of biomedical research at universities in this country were to be trebled, it would still constitute less than 15 per cent of the

*Accompanied by Mr. Edward MacCordy, Associate Vice-Chancellor for Research at Washington University

99-177 O - 82 - 2

current level of extramural research supported by the National Institutes of Health. At the Washington University School of Medicine last year, the federal government sponsored in excess of $50 million in biomedical research and training, and consequently the funds provided in the Monsanto - Washington University agreement - which will amount to $3 million in our initial year of operation in fiscal 1983 - should be viewed in this context; specifically, as a significant supplement to federally sponsored research which provides opportunities to pursue new and exciting fields of investigation.

Before outlining the specific details of the Washington University - Monsanto agreement, it would be useful to remind everyone here today that such arrangements are not new to American universities. In the last century, the Congress firmly established the notion of the Land Grant University and determined that basic research in these universities in collaboration with the agricultural industry would enhance productivity. Subsequently, numerous other examples of university-industry collaboration have occurred in fields other than biomedicine - in engineering, in chemistry, in physics, and, indeed, even in the arts and humanities. We therefore believe that the current trend to develop new university - industrial collaborations is a logical extension of past relationships. Today, there is increased focus on expanding our basic research efforts in biomedicine as well as enhancing the transfer of the results of basic biomedical research to industry - in the hope of accelerating the rate at which useful products and technologies are brought to the public.

We understand and appreciate the concerns of the Committee that these new relationships not distort the principal mission of the university. Universities themselves have already gone to great lengths to make certain that such a distortion does not occur. You are familiar with some of these efforts - the Pajaro Dunes conference, the AAAS symposium, the Committee of the Association of American Univesities (AAU). You can be certain, Mr. Chairman, that we at the universities cherish the freedom in the pursuit of new knowledge that these institutions stand for.

There are major issues that have been confronted in the past by industry and the academy but that continue to be of concern as we move into a new era of such relationships. Several of these concerns have been aired previously in hearings conducted jointly by this Committee and Subcommittee. As I have already mentioned, scientists and administrators at Washington University and Monsanto are intensely interested in protecting those unique qualities of the university: the rights of the scientists to pursue scientific inquiry freely, the public good, and the interests of the company that in the long run will certainly serve the public both through product-development directly and through stimulation of the economy, creation of jobs and new markets for its products.

Now let me review with you the provisions of this agreement and point out to you how I believe that it addresses directly the above concerns. This agreement was developed after a two-year period of extensive

discussions, including a 2 1/2 day science retreat, between Washington University and Monsanto scientists. During this period of time we were all able to develop a clearer understanding of each others' institutional needs and goals as well as the exciting scientific opportunities that lay before us. Monsanto scientists and officials have a very clear concept of the need to preserve academic freedom and information exchange.

The first point I would like to make is that this agreement avoids a direct relationship with any individual faculty member. Its strength centers on the fact that the agreement is at an institutional level. We are therefore enlarging the roles of both institutions in the pursuit of basic and applied research between a research-oriented academic institution and a high-technology industry. This agreement combines these joint resources at an institutional level and should facilitate not only the acquisition of new fundamental knowledge but also its useful application for the public benefit.

Second, the agreement incorporates a system of both internal and external peer review. An eight-person Advisory Committee made of up four senior faculty members of the Washington University School of Medicine and four senior scientist-administrators from Monsanto will solicit research proposals from the faculty-at-large, will review and approve such proposals on the basis of individual merit, will distribute appropriate

funding and will act as a liaison between the University and Monsanto. In the third year of the agreement, and every two years thereafter, a scientific review panel made up of distinguished scientists drawn from the national and international scene and not connected with either institution will review the scientific merit of the projects being funded and the impact of the program on participating institutions. We have, if you will, created a system of dual review comparable in many ways to the system that has served the NIH so well over many years. We believe that this system of review is unique thus far in academic-industrial relationships.

Third, the agreement defines a broad, general area for scientific exploration in which both institutions have complementary expertise and in which we see exciting and promising opportunities for benefitting the public good. The investigative effort will focus on proteins and peptides which regulate cellular function. These substances have a wide variety of biologic functions including: blood clot formation and breakdown; promotion of wound healing; control of inflammation in allergies and various forms of arthritis; activation of the body's defenses to cancer, viral, bacterial and parasitic diseases, and the growth and differentiation of cells, tissues and organs. We also believe that these cell mediator substances have potential for therapeutic use in the treatment of autoimmune diseases, as well as hypertension and neuropsychiatric disorders. The knowledge gained from this collaborative

effort should have important beneficial implications not only for the American public, but indeed for vast populations elsewhere on this globe. In this context, it should be recognized that parasitic diseases constitute the number one world health problem today.

The Advisory Committee will allocate 30 per cent of the funds to exploratory or fundamental research in the above areas. The other 70 per cent will go toward the support of more applied "specialty" projects for which there is significant public need and potential commercial utility in terms of technologies and/or products. Product development itself will be done by the Monsanto Company.

Fourth, the agreement will allow for broad faculty participation predicated on excellence with the aforementioned peer review groups determining which projects are deserving of funding. The guiding rule for this entire effort is that it intersects the strengths and interests of both the University and Monsanto. Monsanto scientists and technicians will spend time in University laboratories learning new techniques and information. On the other hand, Monsanto will provide access to its facilities - such as its isolation and tissue culture facilities - and use of unique biological and other materials to enhance the research productivity of this research collaboration.

Fifth, any financial gain to be derived from this collaborative effort will accrue not to individual investigators, but rather to the institution, to the cognizant department in the Medical School and to the

specific laboratory responsible for the creative effort. The University will hold the patents on any marketable inventions that emerge from the research and Monsanto will have exclusive licensing rights to such patents.

Sixth, under the terms of the agreement, faculty members will be free to publish all results of their findings. Since the University and Company scientists will be working together in a collaborative effort on all projects, the Company will be aware at a very early stage of the possible marketability of any discoveries and will have ample opportunity to assist us in applying for patents. We are convinced that the natural outcome of this arrangement will in no way hamper the free-flow of scientific information.

Thus, Mr. Chairman, we believe that this agreement represents a signficant new step in the evolutionary process of industrial-academic collaboration and that it addresses directly many of the concerns expressed in previous hearings on this issue. Although the specifics of our agreement suit the unique traditional, geographic and scientific characteristics of our two institutions, we do feel that the institutional values and procedures used in evolving this agreement may be useful to other institutions seeking to develop similar collaborative programs with industry.

Thank you very much for your interest and for giving me the opportunity to talk with you. I shall be pleased to answer any questions you may have.

Mr. SHAMANSKY. Thank you for your statement.

We will recess the hearing to go to vote.

[Recess.]

Mr. GORE. The subcommittees will come back to order, please.

Dr. Kipnis, as you may have noted, it s a busy day on Capitol Hill, with all of the bills being considered. We apologize to you and others in the room for the inconvenience.

We will hear now from Dr. Howard Schneiderman, senior vice president for research and development for Monsanto.

Welcome.

Dr. SCHNEIDERMAN. Thank you.

Mr Chairman, members of the subcommittees, in my position as senior vice president for research and development at Monsanto, I am responsible for the functional direction of Monsanto's total research and development activity. Prior to joining Monsanto 3 years ago, I was dean of the School of Biological Sciences at the University of California at Irvine, and I was a member of the academic community for 30 years.

Because of that particular background, I think I understand the academic viewpoint, and in the past 3 years I have come to understand the industrial perspective as well. In my 3 years of sitting in the Monsanto board room, I have discovered that I have not had to give up a single academic vow. My basic value system and the ideas and things I believed in for my entire life as a professor—I did not have to change any of them because I joined a great company.

I have been able to view this recently announced association between Monsanto and Washington University somewhat like a marriage broker. I think I know the good points of both partners, I have seen the defects, I can look at the relationship with a certain amount of objectivity and say that even after the honeymoon, I expect it to be an overwhelming success.

It is an experiment and I hope, Mr. Chairman, that 1 year or 2 years from now you will invite us back to tell you how that experiment is going, and what we have learned from our experience.

I know these hearings reflect a real concern about the value of this kind of association. Many people suspect that a contract between a company and a university threatens the academic freedom to pursue basic research, threatens the academic freedom to publish, and ultimately may undermine the system upon which we depend for the discovery of new knowledge and the training of the thought leaders of the future. There is a concern that industry will encourage universities to pursue excessively utilitarian goals and to neglect the tough, long-term fundamental questions.

Dr. Kipnis and I and our colleagues addressed these issues when we wrote the contract. Your initial remarks were virtually an agenda for the discussions that we had over the first 2½ years. And he has given you his viewpoint on the results of our discussions.

I am confident that we have not only safeguarded the academic freedom of Washington University, but we are enhancing it. We are as concerned as you that the academic enterprise be preserved. We are convinced that our contract not only preserves the goose

that lays golden eggs but will significantly increase its egg production for the public good.

Actually, my purpose in coming before you today is to make a single point. I want you to believe, as Dr. Kipnis and I do, that Monsanto's association with Washington University can be of great benefit to society as a whole as well as to Washington University and Monsanto.

The association between Monsanto and Washington University holds the promise of delivering badly needed health care products to society faster and more efficiently than normally possible. We believe that our contract and our association is in the highest interests of the public.

By combining two of America's greatest resources—the scientific expertise of one of the country's leading medical schools and the technological and scientific capability of a large high technology corporation—we have the opportunity to create new businesses and new jobs, and advance technology. Through this collaboration we expect to discover novel products which address major human diseases and health conditions for which there is presently no cure and no adequate therapy. We view this aim as both socially responsible and commercially attractive.

If successful, a program such as ours will help to increase the international competitiveness of the United States in world markets. Much has been said about the importance of enhancing America's innovativeness. I am convinced that the kind of program Monsanto and Washington University have undertaken will enhance innovation and significantly shorten the time required to take a discovery from the research laboratory and apply it to public benefit.

Associations like the one we are discussing here today have the potential to restore America's leadership in introducing significant new pharmaceutical products into the world's markets.

Monsanto's association with Washington University is part of an orderly plan to bring highly original science and technology to bear on problems of great social and commercial significance. It is a plan to enhance Monsanto's and America's technological competitiveness in world markets by tapping into spectacular research skills of one of our great academic institutions.

In the past year we have seen Congress pass laws to encourage the efficient transfer of technology from American universities to American industry. Industry is, after all, the mechanism that our society has developed for taking original ideas of science and turning them into useful tools to serve society.

This was our feeling when we began talking with Dr. Kipnis and his staff 2 years ago. This drug discovery venture is a result of a long-term love affair between two institutions. We know each other very well. And we understand each of our responsibilities and value systems.

We do not view our agreement for a joint drug discovery venture as a model for other companies and other universities. It was designed to suit our particular institutional cultures. Another pair of institutions would have to design a plan that fits their cultures and their needs. Indeed, the only thing about our contract that I would commend to others is the process by which we put it together.

It is an open contract, openly arrived at. Moreover, we wrote it anticipating problems on both sides, and we addressed those problems in a straightfoward manner. To the best of our ability it is as free of flaws as we could make it.

The goal of the Washington University agreement is to provide society with health care products. Yet at the same time it specifies that 30 percent of the research is to be in pursuit of fundamental biological questions. The other 70 percent is focused on cures for as yet incurable major diseases.

Dr. Kipnis mentioned the joint advisory committee. The presence of this committee permits a broad variety of research to be undertaken. It provides a competitive situation for awarding money. The university gives us a menu of options. It tells the committee what research it is doing or wishes to do, and then the committee selects from among the projects those that it believes have the most promise for solving important health care problems.

If the committee elects not to support a particular project, the university will probably seek other sources of funding. The process resembles closely the process by which competitive NIH grants are awarded. The contract specifies that academic researchers retain their freedom to publish. Washington University sets a 30-day review period for Monsanto to review any manuscript.

One of the attractive features of the relationship is geography. We are only 15 minutes apart. Monsanto is increasing its growth of biological expertise. It will be a true collaboration. We anticipate that Monsanto scientists will be coauthors on a number of the papers that will be published as a result of this joint research relationship. Monsanto scientists will be working in the university laboratories.

Monsanto has the exclusive right to license any patents which may come from the research. The university will convey to Monsanto any rights it is empowered to convey. This is an important point, and it is basic to how effectively this research collaboration will serve its ultimate beneficiary, which is the public.

The strong point of academic research, which you emphasized in your initial remarks, is fundamental research—academic institutions know how to do fundamental research, the "R" if you will of R&D. Industry is also capable of doing highly original research but we are never too proud to accept ideas from elsewhere. The place where industry excels us in the "D" of R&D, the development phase.

Development is an expensive, time consuming, and highly risky process. For every single dollar that a company like Monsanto spends on research to make a discovery, you can estimate that it will take $10 or more to develop that discovery into a useful product which is being manufactured and sold in the marketplace. And there is a rule-of-thumb which suggests that it takes at least 10 years to go from the original discovery to a product on the shelf. This is true of many products. It was true of Astroturf stadium surfaces, developed by Monsanto. Acrilan, acrylic fibers, took us 19 years to perfect. We are presently investigating plant growth regulators. Several of my colleagues appeared before you last week. Monsanto has spent over a decade, and many tens of millions of dollars, and we still do not have an important growth regulator in

the world marketplace. So it is an enormously risky business—many dry holes.

A company cannot afford to invest shareholders' money in the kind of high-risk, high-cost, long-term development process that I have described without some guarantee that if the development is successful there will be an opportunity to recoup the investment.

As I mentioned in my initial comments, I have been able to bring to this association sort of a dual perspective, 30 years of university life and 3 years in industry. I can understand the hesitation that many of my colleagues in universities have, especially their concerns about protecting academic freedom. At the same time, I can see that industries need to insure that they will retain their commerical freedom to develop and market innovative and unique products. But beyond the small individual benefit that may come to Washington University and to Monsanto as a result of this association, I can look at the two partners in this marriage and see the potential benefits that can come to American society in terms of jobs, useful products, American technological capability, and new ways to meet basic human needs throughout the world.

I thank you very much for the privilege of presenting my views to the committee. I will be happy to answer your questions, as will Dr. Kipnis.

[The prepared statement of Dr. Schneiderman follows:]

TESTIMONY BY HOWARD A. SCHNEIDERMAN, SENIOR VICE PRESIDENT, RESEARCH & DEVELOPMENT, MONSANTO CO. ST. LOUIS, MO.

Mr. Chairman, Members of the Subcommittee, Ladies and Gentlemen

My name is Howard Schneiderman. I am Senior Vice President for Research and Development at Monsanto Company in St. Louis. In that position I am responsible for the functional direction of the company's total research and development activities. Prior to joining Monsanto three years ago, I was Dean of the School of Biological Sciences at the University of California at Irvine.

I am a developmental biologist, a member of the National Academy of Science and was a member of the academic community for 30 years. Because of my background, I understand the academic point of view. In the past three years, I have come to understand the industrial perspective as well. For this reason, I view Monsanto's recently-announced association with Washington University somewhat like a marriage broker. I know the good points of both partners, and I have seen the defects, so I can look at this relationship with a certain amount of objectivity and say that even after the honeymoon, I expect it to be an overwhelming success.

I know these hearings reflect a real concern about the value of this kind of association. Many people suspect that a contract between a company and a university threatens the academic freedom to pursue basic research, threatens the academic freedom to publish, and ultimately may undermine the system upon which we count for the discovery of new knowledge and the training of the thought leaders

of the future. There is a concern that industry will encourage universities to pursue excessively utilitarian goals and to neglect the tough, long-term fundamental questions.

We addressed those concerns as we wrote this contract -- those concerns and many more. Dr. Kipnis has already given you his view of the results. I am confident that we not only have safeguarded the academic freedom of Washington University, but, in fact, we are enhancing it. We are as concerned as you that the academic enterprise be preserved. We are convinced that our contract not only preserves the goose that lays golden eggs but will significantly increase its egg production for the public good.

Actually my purpose in coming before you today is to make a single point: I want you to believe, as Dr. Kipnis and I do, that Monsanto's association with Washington University can be of great benefit to society as a whole as well as to Washington University and Monsanto.

The association between Monsanto and Washington University holds the promise of delivering badly needed health care products to society faster and more efficiently than normally possible. We believe that our contract and our association is in the highest interests of the public.

By combining two of America's greatest resources -- the scientific expertise of one of the country's leading medical schools and the technological and scientific capability of a large high-technology corporation -- we have the opportunity to create new businesses and new jobs, and advance America's

technology. Monsanto's ultimate goal is to become a full-fledged member of the health care field. Through this collaboration we expect to discover novel products which address major human diseases and health conditions for which there is presently no cure and no adequate therapy. We view this aim as both socially responsible and commercially attractive.

If successful, a program such as ours will help to increase the international competitiveness of the United States in world markets. Much has been said about the importance of enhancing America's innovativeness. I am convinced that the kind of program Monsanto and Washington University have undertaken will enhance innovation and significantly shorten the time required to take a discovery from the research laboratory and apply it to public benefit. Associations like the one we are discussing here today have the potential to restore America's leadership in introducing significant new pharmaceutical products into the world's markets.

Monsanto's association with Washington University is part of an orderly plan to bring highly original science and technology to bear on problems of great social and commercial significance. It is a plan to enhance Monsanto's and America's technological competitiveness in world markets by tapping into spectacular research skills of one of our great academic institutions. In the past year we have seen Congress pass laws to encourage the efficient transfer of technology from American universities to American industry.

Industry is, after all, the mechanism that our society has developed for taking original ideas of science and turning them into useful tools to serve society.

This was our feeling when we began talking with Dr. Kipnis and his staff two years ago. In those two years of careful planning, which were based on many decades of mutual interaction, Washington University and Monsanto have developed a plan for bringing the benefits of important discoveries made at a great medical school to the public by means of Monsanto technology.

We believe the plan we have devised could greatly speed up the application of important medical discoveries to human ills.

Let me emphasize that Monsanto and Washington University do not view our agreement for a joint drug discovery venture as a model for other companies and other universities. It was designed to suit our particular institutional cultures. Another pair of institutions would have to design a plan that fits their cultures and their needs. Indeed, the only thing about our contract that I would recommend to others is the process by which we put it together.

It is an open contract, openly arrived at. Moreover, we wrote it anticipating problems on both sides, and we addressed those problems in a straightforward manner as the contract was written. To the best of our ability it is as free of flaws as we could make it.

It is important to note that the Monsanto/Washington

University association is also built on experience gained out of other associations with other institutions -- and with each other. About 15 years ago, Monsanto and Washington University entered into a three-way agreement with the Office of Naval Research to do research in the area of high performance composite materials. This program received quite a bit of attention because it was unusual for its time. One of the advantages that Monsanto enjoys today in our relationships with universities is the result of that program. Through that early pioneering collaboration, we developed an organizational confidence and trust that this kind of thing could work to the mutual advantage of all parties.

A later association with Harvard University attracted national attention, and again added to the foundation of understanding which Monsanto brought into the recent agreement with Washington University. Because our 1974 Harvard Agreement was so widely discussed at the time, I'd like to give you a rundown of some of the differences and similarities of the two contracts:

- Both agreements are in the field of biology. The first agreement was drawn up to give our chemical company a "window on biology" and to enhance the public good by increasing knowledge about how human organs develop. For Monsanto, this agreement with Harvard ultimately became the turning point that enabled our executives to think of biology as a major direction for Monsanto to take.

The goal of the Washington University agreement is to provide society with health care products. Yet at the same time it specifies that 30 percent of the research is to be in pursuit of fundamental biological questions. The other 70 percent is focused on cures for as yet incurable major diseases.

- Both contracts were signed between institutions with provision for specific project agreements. However, the Harvard program has remained primarily focused in one area with two principal investigators involved. The Washington University contract, on the other hand, not only builds a framework for specific projects, it also establishes a joint advisory committee made up of four Monsanto representatives and four from Washington University who will decide on research to be pursued. The presence of this committee allows for a broad variety of research to be undertaken, and also provides a competitive situation for the awarding of money. The university tells the committee what research it is doing or wishes to do. The committee selects those projects which it believes have the most promise of solving important health care problems. If the committee elects not to support a particular problem, the university will probably seek other sources of funding. The process resembles closely the process by which competitive NIH grants are awarded.

- Both contracts specify that academic researchers retain their freedom to publish; the Washington University

99-177 O - 82 - 3

agreement sets a 30-day review period for Monsanto over any manuscript.

- Both contracts call for an independent oversight committee. The Harvard oversight committee is made up of a number of leading citizens in scientific, academic and public arenas representing society's stake in the research; the Washington University agreement calls for a scientific peer review committee who will review the work after a set period of time, and assess both its scientific merit and the impact of the program on the two institutions.

- Both contracts encourage mutual exchange of ideas among scientists. However, the physical distance involved and the nature of the Harvard agreement are such that Monsanto sicentists are working separately in St. Louis to provide biological materials to the Harvard laboratories. The associations that grow out of the new contract will be much much closer. Because of the proximity of Washington University to Monsanto -- we are only 15 minutes apart -- and because of the rapid growth of biological expertise inside the company, this will be a true collaboration. Monsanto scientists will work on each project with Washington University scientists, in their labs and in our labs.

- In both cases, Monsanto has the exclusive right to license any patents which may come from the research.

This is an important point, and basic to how effectively this research collaboration will serve the ultimate beneficiary: the public. The forte of academic

research is fundamental investigations: the R, if you will, of R&D. While industry is also capable of doing highly original research, we are never too proud to accept ideas from elsewhere. The place where industry excels is in the development phase -- the D half of R&D. Development is an expensive, time-consuming, highly risky process. For every single dollar spent on research to make a discovery, you can estimate that it will take $10 or more to develop it into a useful product which is actually being manufactured and sole in the marketplace. Not only is this process expensive, it is time-consuming. There is a rule of thumb that it takes at least ten years to go from the original discovery to a product on the shelf. That was true of AstroTurf stadium surfaces which were developed by Monsanto. Acrilan acrylic fiber, another Monsanto product, took 19 years to perfect. To develop plant regulators which will enhance the yield of major crops, Monsanto has already spent well over a decade and many tens of millions of dollars and we still do not have an important plant growth regulator in the world's marketplaces.

So you can see that a company cannot afford to invest shareholders' money in the kind of high cost, long term development process I have just described without some guarantee that if the development is successful there will be an opportunity to recoup the investment.

As I said a few minutes ago, I have been able to bring a dual perspective to this association. I spent

30 years in university life. I can understand the hesitation many of my colleagues in universities have and their concerns about protecing academic freedom. Likewise, I can see that industry has needs to ensure that they, too, will retain their industrial freedom to develop and market innovative, unique products. But beyond the small individual benefit which may come to Washington University and Monsanto as a result of this association, I can look at the two partners in this marriage and see the potential benefit that can come to American society in terms of jobs, useful products, American technological capability, and new ways to meet basic human needs throughout the world.

Thank you for the privilege of presenting my views to the committee. I shall be pleased to answer your questions.

Mr. SHAMANSKY. Dr. Schneiderman, I can't help but note that the optimism and joy which you have approaching this marriage reminds me of a honeymoon. But as a lawyer, I sometimes have seen the ends of not just honeymoons, but of marriages, and not to pursue the analogy too closely, what happens if there is a divorce along the way?

Mr. SCHNEIDERMAN. Well, certainly we will go to a marriage counselor before that happens.

We have had a lot of experience in working together. Indeed, we have interacted for decades, many decades. That is a real advantage.

In the health care area specifically, we have interacted for a number of years. But Monsanto has had many other interactions with Washington University. One of our first scientific interactions with Washington University began some 15 years ago as part of a U.S. Government-Navy, Washington University-Monsanto relationship.

Also, we have had a long-term relationship with Harvard University in health care research, beginning in 1973.

Mr. SHAMANSKY. What I am trying to suggest is not that you haven't had a long relationship, but I am interested in what your agreement provides for if it doesn't work?

Dr. SCHNEIDERMAN. The entire program will be reviewed after 3 years by an external review committee to assess the merits of the scientific work and the impact of the relationship on both institutions.

It will be reviewed every 2 years thereafter and those reports will be given to the chancellor of the university, to the president

and chairman of Monsanto and to members of this advisory board. The committee will monitor the impact of the relationship and the health of the marriage. If it concludes that for some reason the program should be terminated, there are provisions provided for termination in the contract. We are obligated to provide the university with 2 years of advance notice if we wish to end the program.

Mr. SHAMANSKY. I assume, Dr. Kipnis, both parties have that understanding.

Dr. KIPNIS. Yes, the university has the same right and has to provide the same notice.

In addition, there is a clause that within the total complex if there are some very interesting projects the university and the company can continue those in a more restricted fashion for an additional 2 years beyond that point.

Mr. SHAMANSKY. I would like to just pursue this train of thought a bit further. Your agreement apparently provides for Monsanto personnel to work in Washington University laboratories, is that correct?

Dr. KIPNIS. That's right, in accord with university rules and regulations. It also provides for the company to make available all of its resources, personnel, and products necessary to enhance the specific research project.

Mr. SHAMANSKY. What I am asking is, if you look at the amount of R&D money that you get from the Government, which is, as I think you stated, somewhere in the area of $50 million per year, and your arrangement with Monsanto, which is less than 10 percent of that per year, have you given some thought to at least the appearance of Monsanto personnel working in your laboratories and having access to research funded by the public which might be construed as ending up for the benefit of one private company, namely Monsanto?

Dr. KIPNIS. A great deal of thought has been given to that. Let me make some comments that our faculties, as well as our colleagues, have discussed.

First of all, it seems important to us that science be open. The confidentiality with which our faculties deal with Monsanto deals only with the information that Monsanto supplies us, not with the information generated by our faculties.

Mr. SHAMANSKY. If I may pursue that point. Are you saying that whatever you do for the Federal Government in terms of research is equally available to everybody?

Dr. KIPNIS. Everybody, public domain.

Mr. SHAMANSKY. Would you then permit anybody to come in and pick and choose among the research projects—you don't give equal access to everybody to your work on Government contracts, do you?

Dr. KIPNIS. Well, no. But the access within the university is exclusively with research projects being carried out under Monsanto funds.

If projects happen to be in a laboratory where that laboratory also has active research funded by other sources by the nature of being within the laboratory, there is access to general information, but that information is also available on the broad base.

In addition to that, within the contract, there are clear provisions made that the licensing or patent rights that the university offers Monsanto, deals with Monsanto projects and those supported by them.

For the last almost 10 years, Mr. Shamansky, we in academic universities have been subjected to an extraordinary array of auditing processes by the Federal Government to define the specifics of the cost of research, and what research is being done by what funds.

The same kinds of identification that have been accepted by Government auditors are also applied to defining what research Monsanto does and, therefore, has access to.

Mr. SHAMANSKY. Would you be good enough to describe what you mean by peer review in this context and how it might differ from what peer review has meant heretofore?

I am assuming you are putting a different wrinkle on it?

Dr. KIPNIS. No, the standards of peer review deal with scientific excellence and relevance to the program. They are in essence reflecting the experience most of us have been raised with throughout our academic lives in terms of peer review by governmental organizations, such as the National Science Foundation and the National Institutes of Health.

In those cases, the Government defines an area which they wish to support. Research applications are then invited and site teams of experts are brought out to review it in terms of the scientific merits of the proposals and relevance to the field identified.

We intend to apply the same standards in terms of our own internal peer review.

Also, occasions will arise when the expertise of the reviewers is limited and, in those cases, we intend to utilize the same techniques that have been used by Government agencies, namely, seek expert advice by other members within our faculties who then have the same obligation of confidentiality. When outside reviews are sought, these are privileged communications.

Therefore, we want that kind of expertise.

The external review is in the same terms. That is, we want internationally recognized scientists in the areas that are being covered.

Mr. SHAMANSKY. For an internationally recognized scientist to come and review any program, takes his or her time and effort, to travel to St. Louis. I am assuming there is some compensation for that?

Dr. KIPNIS. Yes; within the contract, the costs of that review are borne by the contract itself. I would point out that peer review that many of us are involved in takes a great deal of effort and time, but unless outstanding scientists are willing to contribute their time to do this at modest compensation, the system will not thrive.

Mr. SHAMANSKY. I just want to establish the point when you talk about peer review and contributions of that sort, there has to be some compensation.

Dr. KIPNIS. Yes; the internal peer review is not compensated, external review is.

Mr. SHAMANSKY. And you would expect to pay for those services.

Dr. KIPNIS. Oh, yes.

Mr. SHAMANSKY. I would ask you to comment briefly on some suggestions made by Derek Bok, president of Harvard, regarding universities that accept corporate funds so they will not compromise their academic goals.

I will read part of president Bok's statement here.

"Deny exclusive licenses on university patents to a firm in which a university researcher has a significant interest."

Would you comment? You don't have that in your situation.

Dr. KIPNIS. No.

Mr. SHAMANSKY. But in general, how do you feel about that?

Dr. KIPNIS. I have rather strong feelings about outstanding scientists developing equity positions or assuming directoral positions in companies involved in comparable research. That is excluded in our contract.

As a matter of fact, in the addenda to the contract, the individuals who are applying for funds must reveal to the university advisory committee all kinds of relationships, including research and consultantships, to assure that conflict is avoided.

Mr. SHAMANSKY. You agree, Dr. Schneiderman?

Dr. SCHNEIDERMAN. I agree.

Mr. SHAMANSKY. Let me ask you this question, supposing the guy owns five shares of Monsanto Chemical.

Dr. KIPNIS. Well, it——

Mr. SHAMANSKY. Or a larger amount.

Dr. KIPNIS. We would use the same judgment the NIH does when they ask if you have ownership in a company.

Mr. SHAMANSKY. In other words, it is not a blanket prohibition.

Dr. KIPNIS. Most of us have retirement and I would hope that some of that stock is invested in high-technology companies.

Mr. SHAMANSKY. I would like to read more of president Bok's statement, "Prohibit a professor from simultaneously holding stock in a company, being a consultant to it, and getting grants from it." President Bok says when you pile all those relationships together, you create a far larger incentive for the scientist to work for the firm, rather than the university.

That is consistent with what you are saying, correct?

Dr. KIPNIS. Correct.

Mr. SHAMANSKY. You feel you have taken steps to guard against that?

Dr. KIPNIS. Yes. In the confidentiality agreements, the first statement deals with complete disclosure by the scientist involved so everybody knows what is happening.

Mr. SHAMANSKY. The third part of president Bok's statement you have in effect answered, that is, forbidding professors from owning substantial blocks of stock in a company that might benefit from the research.

Dr. KIPNIS. Absolutely.

Dr. SCHNEIDERMAN. That's correct.

Mr. SHAMANSKY. And that reflects the consensus of your faculty members?

Dr. KIPNIS. We have not held broad meetings within our university, but we have contacted, during the course of these extensive discussions, somewhere between 18 to 20 of our senior professors

and six departments that together account for about 70 percent of the research budget.

Mr. SHAMANSKY. To the extent that you know Dr. Schneiderman, do any of the staff members of the institutions with which you have arrangements have any substantial holdings in Monsanto?

Dr. SCHNEIDERMAN. The institutions that we——

Mr. SHAMANSKY. In this case, Washington University. I am assuming there could be others, but you wouldn't know that.

Dr. SCHNEIDERMAN. No. Except that Washington University's endowment may have some investment in Monsanto, if they don't, they should.

But apart from that, I don't know of any at all, sir.

Mr. SHAMANSKY. The last question I would ask—if I don't ask it, it won't get asked. The nature of our work is that we are supposed to be in two places at one time, of course.

How are you handling the question of getting adequate manpower to work in this biotechnology field?

We have had testimony that up to 50 percent of our scientists and engineers at the Ph. D. level are coming from overseas, and engineers and scientists are being hired into industry at bachelor's and master's levels and not going on to the Ph. D. level.

Are you having trouble staffing these more esoteric areas?

Dr. KIPNIS. May I answer in two parts to that question?

As an M.D. biomedical scientist, I have been deeply disturbed by the contracting pool of M.D.'s willing to commit themselves to traditional academic careers and serious science.

I am sure this committee must have had testimony from NIH and other groups relevant to that important issue.

I don't think there is any one simple answer.

Many of us in clinical departments have been exposed to the lucrative opportunities in private practice.

Now, basic scientists suddenly have exposed to them the same kinds of lucrative opportunities in other kinds of activities other than traditional academic life.

To a certain degree, I think this might be an aberration. I think that opportunities and positions will fill as outstanding corporations like Monsanto develop their own in-house expertise.

On the other hand, some institutions have been more successful in competing for academic faculties and graduate students than others.

In good part, that reflects the commitment of the institution to create an environment which would be attractive to traditional academic values.

When one recruits young staff, one has to be able to provide them with both time and funds to initiate their early scientific careers.

Mr. SHAMANSKY. If I may go one step back, what do you forsee, from your discussions with your fellow faculty members, with respect to the effect on students, on the availability of students, if guaranteed student loans for graduate students are eliminated?

Dr. KIPNIS. I think that is going to have a very deleterious effect on the introduction of young talent into the scientific field.

Mr. SHAMANSKY. You are aware that is scheduled to happen?

Dr. KIPNIS. Oh, yes. We would be happy to provide testimony on what we think is an inappropriate action, namely to fail to reinvest in our own resources, human resources.

Mr. SHAMANSKY. May I suggest you write the Secretary of Health and Human Services and President Reagan among others?

Dr. KIPNIS. Yes, sir, we know their addresses well.

Mr. SHAMANSKY. I have no problem on that one anyway. Frankly, Dr. Schneiderman, you are nodding in agreement and I am glad to see that.

I think it would be appropriate if the head of Monsanto would make those views, if those are indeed his views, known.

Dr. SCHNEIDERMAN. I would have to ask him.

Mr. SHAMANSKY. Yes, but it is your recommendation. What I am trying to say to you is that I think it is a real problem.

You apparently are not in disagreement with that.

Dr. SCHNEIDERMAN. I agree, it is a major problem. A company like Monsanto, on its own account, can do a modest number of things, but we can never conceivably meet the shortfall.

Mr. SHAMANSKY. That is what everybody tells us. At the same time we encourage the companies to do a greater share than they have in the past.

This Congressman at least is convinced that we are not going to make up the difference and it is beginning to look like an American version of the Chinese cultural revolution in which you just wipe out or make it very difficult to train the new cadre of teachers and researchers.

Dr. SCHNEIDERMAN. I associate myself with your remarks.

Mr. SHAMANSKY. Good. You are very wise.

Gentlemen, as you are probably aware, the investigations subcommittee has a keen interest in the contract executed last year between the Massachusetts General Hospital and the German chemical firm of Hoechst.

Aside from the fact this was a foreign firm, which was probably of concern to many of us, when we had the General Accounting Office review that contract, they found that if some faculty member was undertaking research funded by both the Government and Hoechst, there was a potential conflict-of-interest problem.

The problem would arise if the hypothetical investigator was not forthright about a commercially valuable idea being funded in part by Federal money.

What protections do you have in your agreement concerning commingling of funds?

Dr. KIPNIS. May I answer part of that question?

Again, we have spent almost 7 years in intimate contact with a wide variety of Government auditors asking this very question about commingling of Federal funds with academic funds, that is, institutional funds, funds from private health agencies, and other sources.

So that at times, if I may say so auditing requirements bordered on harassment of academic faculties to distinguish between their efforts of teaching and research when they really couldn't.

Nevertheless, we have developed auditing systems which have been acceptable. We feel, therefore, that these systems should be

acceptable for defining the specific research programs supported by Monsanto and in that sense, not commingling the moneys.

Next to me is Mr. Edward MacCordy, assistant vice chancellor at the university who deals in issues of patents, licensing and Government and institutional relationships.

He might be able to comment more intelligently on certain specifics, Mr. Shamansky.

Mr. MACCORDY. One, the moneys from different sources are never commingled as such.

Nonetheless, an invention can derive its financial support from multiple sources and you really cannot determine that until after the invention is made.

In this particular case, the agreement speaks to this issue by acknowledging that if an invention should find joint support from the corporation and from Government sources, that the Government rules and regulations applicable to inventions would apply and the university simply would give Monsanto the best license that it could, which under present law is an exclusive license for a limited term.

Mr. SHAMANSKY. Thank you.

Mr. GORE [presiding]. Tell me briefly exactly why you felt it was a good idea to denominate a particular percentage of this funding for basic research?

Dr. KIPNIS. May I comment first on the definition of "basic" and the terminology we have used?

Mr. GORE. Please do.

Dr. KIPNIS. There is a continuum of research from a basic observation to ultimately a very practical product or technology that is introduced, and that is a long process, but it is a continuous process.

It was clear to our academic faculties that our experience lies in research, not in development.

From the beginning, that definition was accepted by all. Within our own institution, we have arguments when somebody says they are a basic scientist and somebody says they are a clinical or applied scientist.

It is our belief that what is in basic science departments today should be part of the scientific body of our clinical departments within 5 years.

The operating definition we use for basic or exploratory research is to observe new fundamental phenomena and, therefore, we don't use the word "basic," but we use the word "exploratory," that is one group of projects.

The other group are so-called "specialty projects" where the scientific effort has been brought to the point where studies now can be done to define the relevancy of those observations to areas of human physiology, normal or abnormal.

That we believe is a special kind of exploration. When that is carried to the degree where a decision has to be made whether this is a useful potential area for product development, that now is up to the company to make that decision.

In initial contract, half the money is earmarked for basic science and half for specialty projects. That is the split now.

We would be willing to bet that if other scientists looked at what we are calling specialty projects and basic science projects, they would have a hard time distinguishing whether they were not all basic.

Again this reflects the attitudes of our own faculties. We have built in an increase in the basic science with the recognition that we expect many of the basic science projects after 3 to 4 years to be converted to a specialty project.

It is our assumption that at the end of the 4- or 5-year period when we have reached the mature relationship, about 30 percent will be basic, 70 percent specialty.

Dr. SCHNEIDERMAN. May I piggyback on his remarks?

Mr. GORE. Yes, please.

Dr. SCHNEIDERMAN. A basic research project would be how chromosomes work, how genes are regulated.

In our context, a specialty research project would be an identification of a cure for an incurable major disease.

It is hard to draw the line. Let me use an example from agriculture, which isn't the subject of this agreement. A great challenge in agriculture research would be to develop wheat, or corn that didn't require nitrogen fertilizer.

Now, is that a fundamental or an applied piece of research? I am sure there is a Nobel prize in it. But I think it is both. I can't distinguish between the basic applied in that case.

When it comes to product development, that is not the role of the university. Product development and all of the extensive work that goes into it is an appropriate activity for a company.

Mr. GORE. Does the independent board have any decisionmaking power over the course of research or is it merely an advisory board?

Dr. SCHNEIDERMAN. The independent board is an advisory committee composed of four Monsanto people and four Washington University people who oversee the program.

The role of that committee is to ask the university what it has to offer. From that list of options, it selects appropriate projects.

The committee would certainly not be involved in directing the research. It will assess the results of the research, and I dare say that if in 3 or 4 years the results are not promising, the committee may say, well, have you tried other approaches?

But not in terms of the direction of the research.

Mr. GORE. Who says what do you have to offer?

Dr. SCHNEIDERMAN. The committee.

Mr. GORE. The committee says to the university, what do you have to offer?

Dr. SCHNEIDERMAN. Yes.

Mr. GORE. And the university gives the committee a menu?

Dr. SCHNEIDERMAN. Yes.

Dr. KIPNIS. An area of science is defined, proteins and peptides regulating cellular function, for example.

The committee will disseminate an RFP during the summer indicating the area of science and describing in detail the fundamental molecular areas that might be involved as well as the very clinical applied areas.

We invite people on the faculties to submit research projects which will be reviewed on the basis of scientific merit and relevance.

Mr. GORE. And then——

Dr. KIPNIS. They will be approved and they are to be reapproved annually because most of the projects will be assumed to be of a long-term basis. We expect to have the same kinds of application forms as the NIH research grant and the same sort of annual reporting that they have.

Mr. GORE. Now, the advisory board then, or the committee, then looks at the menu and either approves or disapproves?

Dr. SCHNEIDERMAN. That's right.

Mr. GORE. And that is for both basic research and applied research?

Dr. SCHNEIDERMAN. Right.

Dr. KIPNIS. Yes.

Mr. GORE. What the board chooses will be pursued by the university and what the board turns thumbs down on will not be pursued by the university?

Dr. KIPNIS. Oh, no.

Dr. SCHNEIDERMAN. No.

Dr. KIPNIS. Our investigators have great ingenuity in finding funds from some sources. If they want to do something——

Mr. GORE. It will not be pursued by the university under this Monsanto contract?

Dr. KIPNIS. That's right. Under the Monsanto contract, no.

Mr. GORE. The university members of the board are who?

Dr. KIPNIS. Four chairmen of departments.

Mr. GORE. The chairman of the department, OK, and who else?

Dr. KIPNIS. There are four chairmen. I am a program director and I am chairman of the department of medicine, the others are the chairmen of the departments of immunology and chemistry, microbiology and pathology. They are the four professors that will be sitting on the committee and able to seek other advice. The four members of the company are senior scientist officers, Dr. Schneiderman, Dr. G. Edward Paget, Dr. Louis Fernandez, and Dr. David Tiemeier.

Mr. GORE. So there are four from the university and four from the company.

Dr. KIPNIS. That's right.

Dr. SCHNEIDERMAN. Yes.

Mr. GORE. No research can be conducted with the Monsanto money unless it is approved by the board which is 50 percent controlled by the company and 50 percent controlled by the university.

Dr. KIPNIS. That's right.

Mr. GORE. Even basic research?

Dr. KIPNIS. That's right.

Mr. GORE. How are tie votes resolved?

Dr. KIPNIS. Why don't you speak to that?

Dr. SCHNEIDERMAN. We are counting on consensus. This is a partnership and a partnership means that you work on things that make sense from both sides.

I am sure that there will be some things that Monsanto is very interested in that Washington University will not have on its menu.

I am sure that there are some things that Washington University is deeply interested in, and thinks are vitally important, that Monsanto does not have on its menu.

But there will be some common areas and we will work from that.

We will work on those things where we have agreement and can do something useful. If this agreement is to be renewed and to last for 10 or 15 years or longer, and be an important part of the fabric of both institutions, it has to be valuable to both institutions. They have to agree on things like that.

So we have to come to agreement. I have no doubt that we will have areas of disagreement, but I think that most of the time, we will identify some things that we can productively spend our resources on.

Dr. KIPNIS. During the course——

Mr. GORE. Wait a minute, just to get a response to the specific question, is there no mechanism for resolving tie votes should they occur?

Dr. KIPNIS. No. As a matter of fact, I must point out to you that in the rather extensive discussions that went on for over a year, including those in our office, about whether we should have five, four, six, two, three, one, et cetera, two of the academic faculty who were the most vociferous about academic freedom, said, look, if this is a partnership, it has got to be a partnership, so let's have equal votes.

If we don't have success, then the contract isn't going to be worth much.

Dr. SCHNEIDERMAN. I think the term "marriage" is appropriate in that context.

Mr. GORE. The history of both partnerships and marriages would give some pause for concern, but——

Dr. KIPNIS. That has not escaped our attention.

Mr. GORE. All right.

Now, the advisory committee will allocate 30 percent of its funding to basic research, as was noted earlier. Before the agreement was signed, what percentage of university R&D in this area was devoted to basic research?

Dr. KIPNIS. Again, I don't wish to beg off answering that, but I would tell you the kinds of problems we had. Our department of medicine at the present time has close to $20 million of research. This is out of a total university or medical school funding of approximately $50 million.

Now, if you would ask a professor of anatomy what goes on in the department of medicine, he may well say that it is clinical applied research.

Many of my staff who have their Ph. D.'s, as well as M.D.'s, and are training Ph. D. students, would be upset to be called applied rather than basic scientists.

So I wish to just say that there is no way we could account for how much is basic and how much is applied.

Mr. GORE. Would you say that 70 percent has been applied in the past?

Dr. KIPNIS. I would say that, again the definition of what we use as specialty projects is not applied. We just merely say it is basic science which has a greater identification.

It is not as amorphous as a fundamental research project is. I am not trying to beg an answer, but this is the quandary we get into, even at the NIH, when we argue about what is clinical, what is applied, and what is basic.

Dr. SCHNEIDERMAN. May I respond to the question, Mr. Chairman. If you were to look at what the university would be doing 5 years from now, using whatever metrics you may have for what is "applied" and what is "basic"—I do not believe that this relationship is going to alter the relative proportions of "basic" or "applied" research done by the university.

Mr. GORE. Back to the tie vote briefly, if there is a tie vote, then presumably, it would not go forward?

Dr. KIPNIS. That's right.

Mr. GORE. So a university researcher wishing to conduct basic research must get the acquiescence of at least one company official on the board before it can proceed?

Dr. KIPNIS. Sure.

Mr. GORE. Even basic research?

Dr. KIPNIS. Surely.

Mr. GORE. All right.

Now, members of the faculty will be working with Monsanto, is that correct?

Dr. KIPNIS. Yes.

Dr. SCHNEIDERMAN. Yes.

Mr. GORE. What if they find out in the course of their work information from the company that is proprietary in nature and this information becomes commingled with the ongoing research effort?

Are you concerned about that?

Dr. SCHNEIDERMAN. Provisions have been made. They will sign an appropriate confidentiality agreement and agree not to convey to others, unless through inadvertence, information of a proprietary nature that belongs to Monsanto.

I am talking about recipes, not fundamental knowledge.

Mr. GORE. So members of the faculty at Washington University will be required to sign confidentiality agreements in advance?

Dr. SCHNEIDERMAN. The same agreements, for example, that we undertake when we review an NIH grant, or something of this kind, in which we simply assert that we will not tell any competitive investigator what professor X is doing.

It is the same kind of agreement not to convey private information.

Mr. GORE. What about testimony we have had in the past about scientific symposia where university researchers who would otherwise feel free to express themselves verbally are constrained by lawyers now: Don't say this, don't say that.

The concern raised in other previous hearings is that this has an effect on academic freedom.

Does your agreement deal with any restrictions on the university professors expressing themselves verbally at scientific symposia or something of that kind?

Dr. KIPNIS. No. They are allowed and encouraged to actively participate everywhere. The only limitation that is defined is that we will provide the initial drafts of any publication of research that has been accomplished under Monsanto's support for review for 30 days to establish patentability.

Mr. GORE. Well, now let me ask you to consider the question again with reference to the agreement itself.

Do you have a copy of that?

Dr. KIPNIS. Yes.

Mr. GORE. This is page 23, paragraph 9.3.

We don't intend to divulge the contract itself, consistent with the agreement that we have with you.

Dr. KIPNIS. I understand.

Mr. GORE. But for this question, it does appear in that paragraph that the company and the university tend to provide guidelines on withholding verbal discussion of certain research findings.

Am I reading that wrong?

Dr. KIPNIS. No. Maybe you should address this?

Mr. MACCORDY. The key word is "divulgation" which relates—although it is not specifically mentioned—primarily to European patent law, which has a different standard of divulgation to the public.

In other words, under our law you can publish or otherwise divulge to the public an invention and even under worse-case situation you have a 1-year grace period in which you can file for patent rights, under European law, that is not true.

A simple speech to the public can immediately compromise all of your patent rights.

Mr. GORE. I understand that and companies in this area are interested in getting patents, not only here, but worldwide, and the standard in other countries is different and if someone stands up in an academic forum and freely discusses his or her research, then that may have implications for the ability of Monsanto to get a worldwide patent on the results of that research.

Now, that makes it obviously a trade-off situation. What I am exploring here, without making value judgments, is how that trade-off has been made.

It appears that it has been resolved in a way that will allow the company to put guidelines on or provide guidelines for university professors and researchers as to what it is all right for them to speak about in an academic forum or any other context.

Is that correct?

Dr. SCHNEIDERMAN. Both the university and Monsanto, would provide guidance. But, Mr. Chairman, if, for example, there were a particular molecule that cured arthritis and an investigator discovered the sequence of amino acids in that molecule and we wished to patent that, molecule, so that we could pursue it commercially.

Between the discovery of that piece of information and putting a product on the shelf is $50 million worth of development activities. If the discovery was placed in the public domain before Monsanto could obtain a patent-protected license, I do not think I would be

behaving appropriately toward the shareholders of the company if I were to invest the $50 million in something on which we could not get some patent protection.

Furthermore, I do not believe that that important anti-arthritis drug would reach society.

Mr. GORE. I understand your point of view and I understand the interest that you are expressing.

All I am saying in my question is that there are competing values on the university side and how you subordinate one to the other is of some consequence.

Dr. KIPNIS. I think there are two issues that should be brought in that are related to the very important point you are making.

It is to a certain degree a dilemma. One is to think that communication has always been open between all scientists.

I think that another very important factor in the integrity of the science has been the ego of scientists and the importance of being first.

Mr. GORE. The what? What?

Dr. KIPNIS. The ego of scientists and the pride of accomplishment. Very rarely do scientists always communicate all details of the information until the story is complete.

Another is that many of the instances that have occurred in recent years where freedom of exchange has been hampered involved circumstances where the scientist had an equity position in the field in which he was operating.

We try to avoid that in our own relationships. That is not to say that avoiding it answers the important question you have raised.

But I do think it is important to point out that instances where it has occured have frequently involved equity positions of either the university or the scientist himself.

Mr. GORE. You have already taken a strong stand against those equity positions?

Dr. KIPNIS. A personal one, and many of our faculty feel that way as well.

Dr. SCHNEIDERMAN. Yes, Mr. Chairman.

Mr. GORE. In 1973, Monsanto concluded an agreement with Harvard on biological research. During the 9 years between these two agreements, there has been a lot of discussion on the issues that they raised.

Is it fair to say that this recent contract reflects some of the learning process that the company has gone through in those 9 years, Dr. Schneiderman?

Dr. SCHNEIDERMAN. Yes; I think it reflects the learning process, it reflects changes in American culture, also it reflects that we are working with a different institution, an institution that is only 15 minutes away and with which much more intimate collaboration is possible.

So it reflects a number of things. But your initial comment is correct. That was a very important experience base for Monsanto to have and we have learned from it.

Are there specific issues I have not addressed?

Mr. GORE. Are the priorities, are the projects approved by the basic research projects approved by the board, will they be open, public knowledge?

Would you have some restriction on divulging what it is that you are researching?

Dr. KIPNIS. No. As a matter of fact, within our own school, we have distributed to our executive faculty a description of the kinds of experimental approaches, as well as fields in which basic science should be encouraged.

We have not defined the projects because we don't have the applications to review.

But we have defined a very broad area from the point of gene expression to the point of where these materials act and how they act and clinical studies.

Mr. GORE. Mr. Weber.

Mr. WEBER. Thank you, Mr. Chairman.

First of all, I would like to say this is the second set of hearings that I have been able to participate in on this general topic.

We did the same thing last year and without claiming any great expertise on it, I want to say that I generally think that what is happening with you folks is a very exciting development.

Although there are certain questions that have to be raised, I personally hope that the Government doesn't come in and mess things up for you.

I would like to ask you to share with me a little bit of your vision on how this is going to develop in one particular area.

We have at the University of Minnesota, as you are probably aware, one of the finest chemical engineering departments in the United States. Some of the priorities in terms of funding for the university reflect that, the laying off of employees in times of austerity reflects that, and so on.

However, the Twin Cities community is technology-based, and probably has a greater demand for other types of engineers.

I have been involved in discussions lately with people who are interested in trying to influence the university into changing its emphasis away from chemical engineering towards the types of engineering that are more appropriate to the Twin Cities' economic base.

I say that as a preface to my general question. I would like to ask you if you see, as a result of what you folks are doing, more and more adaptation on the part of universities to the specific economic base of the communities in which they exist. If so, will that be a good thing or bad thing?

Dr. SCHNEIDERMAN. May I respond to that. Let me use chemical engineering as an specific example.

Monsanto employs thousands of chemical engineers.

Chemical engineering curricula at universities are changing constantly. Universities are recognizing increasingly the importance of biochemical engineering and fermentation, things of this kind. I am sure that those subjects will be incorporated into the curriculum.

After all, a chemical engineer is not being trained for his first job. A young man or woman who graduates today will be spending more than half of his or her productive life in the next century. They should get a sound basic education, in chemical engineering, not geared to some narrow metric about what the jobs are today.

99-177 O - 82 - 4

On the other hand, chemical engineers should certainly be sensitive to to the needs of specific geographical areas. I suspect that those young men and women who acquire the special skills that a community needs will get the jobs. I believe that natural selection will occur.

Retooling of chemical engineers is also important. Monsanto has established a program to take experienced chemical engineers and send them for a year or 2 to graduate schools to get a master's degree in fermentation engineering so that they can work in that field.

Chemical engineers today have continuing education ahead of them for the indefinite future.

Dr. KIPNIS. I might comment personally, my closest colleague is a professor of biochemistry. We both spent 4 years with a Nobel laureate in chemistry and his son is now a graduate student in the Department of Medical Engineering in Fermentation at the University of Minnesota, having selected that as one of the major centers.

So it is of interest that I am aware of that. I think one of the worst things that can happen is for a university to try and predict what kinds of training and specialty areas will be needed in the future.

The great advances in every field come from areas sometimes least expected and I think rigorous training in fundamental sciences in different arenas are the best way of assuring vitality of your research establishments.

From my own departmental point of view, as a professor of clinical medicine, one of the most anti-intellectual and negative influences on productivity is to assume that cardiologists or gastroenterologists should train the next generation in science.

Those people have to go back and get fundamental science training in physics, and physical chemistry, as well as training for productivity.

So I would think the wisdom of universities should be to support fundamental training of high quality. The individuals will utilize that information most creatively once they are put into positions where they have to use it.

Mr. WEBER. In view of that, do you think there is a danger as the ties between research facilities and industry become closer. Will there be a tendency for the research facilities and universities to narrow their focus in a dangerous way?

Dr. KIPNIS. I think it depends on the nature of the university and the corporate group they are relating to. One of the things we did is we did not define a project and we did not define a product or a technology we were interested in.

We defined a broad area of science and immediately involved genetics departments, immunology, biochemistry, pharmacology, pathology, medicine.

These are areas of scientific training to bring skills to these areas. We train people in the same way.

Mr. WEBER. In the area of agricultural study, my State is a case in point. One can see that there has been a partnership for a long time. It certainly has been a positive one for both parties over many, many decades in my judgment. I guess my predisposition

would be to say we would expect the same thing in university-industrial relations in other areas.

I have no more questions, Mr. Chairman.

Mr. GORE. Mr. Volkmer.

Mr. VOLKMER. Thank you, Mr. Chairman.

I would just like to address—I am sorry I was not able to be here, but I have other committee meetings going on at the same time and just got a notice I have to go back in a few minutes, but I would like to address a few points from the discussions which may not have been thoroughly discussed yet.

First, I would like to know, as I noticed, the contract is between Washington University as an institution and Monsanto, and not with any individual doctors at Washington University.

Dr. SCHNEIDERMAN. Right.

Mr. VOLKMER. As I understand from the testimony, there is no question in your mind that you believe this is a lot better than having contracts with individuals; is that correct?

Dr. KIPNIS. Yes, sir. We thought that to introduce large funding into single laboratories has a devisive nature and discredits the traditional process.

We would prefer to have funds competed for by the faculty at large on the basis of scientific excellence rather than to have a single large area developed which can distort the process.

Mr. VOLKMER. In reviewing the program developed, I think that both parties have done a tremendous service to both the industry and the academic community in showing how something can be developed with the committee system and also the peer review process, which would be completely objective in nature.

The other area I would like Dr. Schneiderman to address is the fact I know that Monsanto basically has had a large research and development operation, but what would be the possibility of this type of research being done using only in-house personnel to the extent you propose here in the biomedical field.

Dr. SCHNEIDERMAN. It would be impossible, Congressman, absolutely impossible. I can't think of any company or consortium of companies in the entire world that could accumulate the talent we have at any one of several great medical schools in the United States.

There is just no way that we can do it.

We simply would not engage in that kind of work.

Mr. VOLKMER. As I understand, the division between the parties in the contract is the ultimate objective of bringing more medical treatment, knowledge for treatment of various diseases to benefit the public.

That is the ultimate goal?

Dr. SCHNEIDERMAN. Central. Particularly diseases for which there is presently no cure.

Mr. VOLKMER. Thank you.

I wish to commend both of you for the contract and wish you well. I wish you success in future years.

As I envision, also, it may go beyond the 5 years, is that correct?

Dr. SCHNEIDERMAN. That is the intention, sir. We want it to work. We are going to do our best to make it work, and we hope it

will become an enduring part of the fabric of both the company and the university.

Mr. VOLKMER. I have no further questions, Mr. Chairman.

Mr. GORE. I just have one brief followup line of inquiry on this matter of control, it is four and four and no research can be conducted without approval of the committee. Four from the university, four from the company.

One of the four from the university must be approved by the company, is that correct?

Dr. KIPNIS. The director of the program.

Mr. GORE. If the program director is not acceptable to the company, then the company can immediately suspend all financial support for 1 month and if it continues for 6 months, then the contract is considered breached. Is that correct?

Mr. MACCORDY. No, there is a phrase in there that says the company shall not unreasonably withhold its approval.

Mr. GORE. So it is a question for litigation?

Mr. MACCORDY. No, it is a question that the company would be required to come up with substantial grounds for not approving, on a scientific basis, that individual.

We don't anticipate that happening.

Mr. GORE. If it did, it would be litigable?

Dr. KIPNIS. We would suggest if the litigous system has to be involved, the contract will not work.

Mr. GORE. Well, I hope that is something that never occurs, but my point is that one of the four university participants has to be acceptable to the company and has to be either approved or not unreasonably denied.

Dr. SCHNEIDERMAN. Yes.

Mr. GORE. OK. It is very, very interesting and your cooperation with the subcommittee is something we greatly appreciate.

We also appreciate your response to our questionnaire and letting us examine your contract and providing your testimony. Moreover, I want to commend you for the effort and thought that you put into this agreement and the effort to try to address the questions that troubled a lot of folks, particularly in the university community.

I think as a result of these exchanges, undoubtedly some will have questions that remain, but we appreciate your willingness to come and discuss it openly and help to focus this inquiry.

Thank you very, very much.

Dr. SCHNEIDERMAN. Thank you very much.

Mr. GORE. Our second panel consists of two witnesses, Albert Meyerhoff, senior attorney with the Natural Resources Defense Council in San Francisco, and Dr. Charles Hess, dean of the College of Agricultural and Environmental Sciences, University of California at Davis.

I would like to welcome both of you to this inquiry. We appreciate your attendance and without objection, the entire text of your prepared statements will be included in the record in full.

We would like to begin with you, Mr. Meyerhoff.

STATEMENTS OF ALBERT H. MEYERHOFF, SENIOR ATTORNEY, NATURAL RESOURCES DEFENSE COUNCIL, SAN FRANCISCO, CALIF.; AND DR. CHARLES HESS, DEAN, COLLEGE OF AGRICULTURAL AND ENVIRONMENTAL SCIENCES, UNIVERSITY OF CALIFORNIA AT DAVIS

Mr. MEYERHOFF. Thank you, Mr. Chairman.

I am Albert Meyerhoff, an attorney with the Natural Resources Defense Council. For the past several years, I have been deeply involved in issues concerning the effects, both positive and negative, of what is now referred to as the commercialization of research at American universities.

I know that the subcommittee, in its previous hearings, has heard substantial testimony on a number of the broader policy questions involved here so I have chosen to structure my remarks somewhat specifically, focusing on three areas.

First, the Calgene case, not because it is unique, but rather because it presents an excellent case study demonstrating that without adequate safeguards, the involvement of industry at universities can result in threats to academic freedom and the potential misuse of public funds.

Second, I would like to address what I believe has been the wholly inadequate response by the university community thus far to the troubling public policy questions that have been raised concerning the "commercialization" of publically financed research, especially in the areas of conflicts of interest, leveraging of exclusive patents rights and protecting graduate student education.

Finally, I would like to urge the subcommittees to seriously consider recommending legislation conditioning the receipt of Federal research funds by American universities on the adoption of a model code of ethics addressing the inherent conflicts of interest resulting from commercialization of research.

Let me start with the Calgene case.

As you know, throughout the Nation, but especially in California and in the Boston area, genetic engineering firms have been springing up adjacent to campuses. In California, up and down the State next to nearly every major research campus, there are now such firms founded and staffed by university scientists.

Frequently they are engaged commercially in work at least parallel to the research conducted in their university roles with public funds. One scientist close to the field estimates that nearly 100 percent of the top people in biotechnology are now tied to one firm or another.

Indeed, one commentator analogized the situation to the original version of the movie, "The Invasion of the Body Snatchers"—you look into a scientists' eyes and realize it is too late.

The Calgene case presents a good case in point. Calgene was cofounded by Ray Valentine, who was also its vice president. Dr. Valentine is a distinguished scientist who has done research into nitrogen fixation. This is the ability of plants to fix nitrogen from the air thereby eliminating the need for chemical fertilizer. Obviously, this presents an area of tremendous economic potential.

Mr. Valentine's work was to be funded by a $2.3 million grant from Allied. This was the largest private grant, I believe, in the

history of the college of agriculture at UC; at least it was equal to all other grants and contract funds provided to the college of agriculture last year combined.

The grant was earmarked to fund five investigators over 5 years, one of whom was to be Professor Valentine.

Within days of the Allied grant to the University of California, Allied purchased a 20-percent interest in Calgene for something over $2 million. When these facts became known there was reaction both within and outside the university. Within the university, a series of letters which I have submitted separately to the subcommittee were forwarded to various university officials expressing alarm about the potential contamination of the research function at the University of California by this close relationship with Calgene. There also were distributing reports that graduate students were unable to complete their graduate education because of the interaction between Calgene and the university.

Perhaps the most eloquent document on the subject—and I would like to just briefly read a portion of it—was a memorandum to Dean Hess from Dr. Emanuel Epstein, a distinguished member of the UC faculty and, to the extent that labels apply here, generally a man of conservative tendencies. He states, in a memorandum dated November 1981:

> In the past it was the most natural thing in the world for colleagues to swap ideas on the spur of the moment, to share the latest findings hot off the scintillation counter or the electrophoresis cell, to show each other early drafts of papers, and in other such ways to act as companions in zealous research.
>
> No more. Any UCD scientist with a promising new slant for the improvement of nitrogen fixation or the enhancement of salt tolerance of crops or accelerated in vitro culture of plant tissue will think twice before talking about it to anyone who is connected with either of the two Davis crop genetic private enterprises, or even with colleagues who in turn might speak to any such person. I know that this type of inhibition is already at work on this campus.
>
> In addition, graduate students of faculty members connected with these businesses are in danger of being directed in ways more tailored to the requirements of those enterprises than the students' educational and professional advancement.
>
> I therefore have my doubts about any very positive approach to this development. I feel that in any statement on this problem by the university the inevitable damage to the academic enterprise that I have discussed here should be clearly spelled out. In effect, what this intimate connection of some of our faculty with corporate business is doing amounts to no less than an insidious but nonetheless real abridgement of the academic freedom of all members of our college and their graduate students. That, I believe, is the main issue that must be confronted.

Around the same time that these facts concerning the relationship between Allied, Calgene and the University of California were becoming public, we were involved in related discussions with the State's Fair Political Practices Commission. The FPPC was established pursuant to an initiative passed overwhelmingly in California known as proposition 9. It is now known as the Political Reform Act of 1974; and was a post-Watergate response to conflicts of interest issues in government.

After several letters to the Commission were to no avail, we filed a formal complaint in August of 1981, urging that the Political Reform Act be made applicable to university scientists, in particular to research decisions. That petition included the facts of the Calgene case.

There were a number of other cases that were before the commission. One involved Genentech and the involvement of UC Prof.

Herbert Boyer, its cofounder. Other university faculty members now have stated publicly that Genentech was actually established in the laboratories of the University of California at San Francisco. At one point, "Genentech's Boyer" provided a grant of $200,000 to the "UC Professor Boyer," seeking exclusive patent licenses for any developments resulting from the use of that grant money.

Another case involved a company known as Engenics, a joint venture by a number of multinational corporations that entered into an agreement between Stanford, the University of California, and this umbrella organization. The facts about that case are still being developed. What is known is that a number of UC faculty members perforing the research also are officers or investors in Engenics, which will receive exclusive patent rights to their discoveries.

The Valentine situation was resolved when Professor Valentine was given the option of either severing his relationship with the Experiment Station, leaving the research project, or severing his relationship with Calgene. He chose to resign from the research project. However, according to reports in the press, at least 30 University of California scientists continued to consult for Calgene. And even after Professor Valentine left the research project, there have been continuing problems, particularly involving graduate students and their required involvement in work being conducted both at Calgene and the University of California.

At the Fair Political Practices Commission meanwhile, a series of hearings were held. Witnesses from around the State testified. At the first vote the commission voted to apply the Political Reform Act to the University of California, rejecting arguments that to do so would in some way abridge academic freedom.

In a second action this March, final regulations were adopted by a 4 to 1 vote which would require, among other things, disclosure by all university scientists of any financial interest they have in private corporations funding their university research through gifts, grants, or contracts.

In addition, in situations where such a relationship existed, those scientists would be foreclosed from participating in research decisions and, instead, would delegate such responsibility to a committee, in the nature of peer review.

These regulations very recently became legally effective in California, after approval by another governmental agency, the Office of Administrative Law. Whether they will be tied up in the courts or not remains to be seen.

The response nationally of the university community to issues of conflicts of interest has been, in my opinion, singularly unimpressive. A conference was held last March at Pajaro Dunes, a secluded retreat near Monterey, Calif. At that conference the presidents from MIT, Harvard, Cal Tech, Stanford, and the University of California, met with 11 presidents of high technology corporations—Du Pont, Eli Lilly, Genentech, Biogen, and a number of other firms. Hand-picked members of the faculties of these schools were also permitted to attend, chosen principally for their ties to business ventures.

No other member of the public was invited. No representation was allowed by anyone from labor, the health care field, from envi-

ronmentalists, consumers, or any other segment of the public frequently directly affected by the impacts of new technology financed by these joint ventures. The press also was excluded.

But more important than the narrow makeup of the conference was what I believe to be its disappointing result. The statement issued by the conferees has been roundly critized in a series of editorials, including the Washington Post, Los Angeles Times, and a number of other commentators. Essentially the document was a series of platitudes that failed entirely to address such central questions as disclosure of financial interests preventing conflicts of interest, and leveraging exclusive patent rights.

I also have kept tabs on what other universities are doing around the country to deal with these issues. Thus far there has been very little serious effort. At Stanford, a faculty committee recommended a reasonably modest conflict of interest policy that would require some disclosure and some disqualification in certain very serious cases. That was voted down overwhelmingly by the faculty. No financial disclosure requirement has been adopted at MIT, Harvard, Johns Hopkins or, to my knowledge, any other major research institution in the country.

At the University of California, faculty are now disclosing financial interests in benefitting companies. I am sure Dean Hess and I will disagree over the motivations for actions taken there. But for over 8 years the university fought the conflict-of-interest law in the courts, first as it applied to the University of California's regents, then to its higher level officials and finally to its scientists.

In short, I think the introduction of strong commercial motivation at universities directly affects "what questions are asked," what kinds of research are done. Given the ever-increasing importance of technology in our society, the public has a right to know that those decisions are being made in their interest, and not in the private interest of the decisionmaker.

We have cases in California where public funds were used to develop a smaller almond for Hershey bars, because Hershey's was making smaller chocolates. We have work being done now to develop "tomato chips," "tomato soap," and "tomato bread" because there is a glut on the tomato market. I have some question why tax money should be expended to develop tomato chips.

The president-elect of the AAAS, Anna J. Harrison, recently commented, that it is time to recognize that all new technology has its beneficiaries and its victims. Too frequently the beneficiaries influence the key decisions, but the silent victims bear the consequences.

If decisions to go forward with publicly funded research turn principally on the commercial potential of that research, where is the public's role? While I know this is not the subject before the committee this morning, I can think of numerous examples of work being done on robotics, nuclear power, alternatives in pest control between chemicals and other kinds of controls, in which the public has a serious stake in a democracy, vesting authority to make such decisions, utilizing enormous sums of public funds, in the industrial sector alone would be a serious error.

The California model in effect now does not apply to private universities. It, of course, also does not apply outside the State of Cali-

fornia. Therefore, we would urge that the subcommittees seriously consider urging legislation which would condition the receipt of Federal grant funds from NIH, NSF, USDA, DOE and other Federal funds, to both public and private universities, on the adoption of a code of ethics. Such a code would, at a minimum, require public disclosure by any university scientists expending public funds of their interest in business entities that could benefit from that research.

Thank you, Mr. Chairman.

Mr. GORE. Thank you very much.

[The prepared statement of Mr. Meyerhoff follows:]

Testimony by

Albert H. Meyerhoff
Senior Attorney
Natural Resources Defense Council
(NRDC)

Mr. Chairman, it is my pleasure to appear before the Subcommittee this morning on behalf of the Natural Resources Defense Council (NRDC). For the past several years, I have been involved in issues concerning the effects, both positive and negative, resulting from the increased infusion of private capital for university research. Insofar as the Subcommittee has previously heard substantial testimony on the broad policy issues involved in the commercialization of university research, I have chosen to structure my remarks somewhat specifically, focusing on the following areas. First, I will briefly address the Cal Gene/Allied Corporation case at the University of California. While not unique, this case study demonstrates quite plainly that without adequate safeguards and public scrutiny, the introduction of strong commercial motiviations into university research tends to threaten academic freedom and invite the misuse of public funds. Second, I will address the thus far inadequate effort by major research universities, both individually and collectively, to deal with a host of important matters presented by commercialization of research, such as conflicts of interest, leveraging exclusive patent rights and the protection of graduate student education. Third, because the overwhelming

bulk of research funds are provided by the taxpayer, I will address the need for consideration of federal guidance here, especially in the area of conflicts of interest.

(1) The Cal Gene - University of California Case

As you have heard previously, throughout the nation but especially in California and around Boston, private genetic engineering research firms are springing up adjacent to universities, established and staffed by university scientists, who are performing for profit work sometimes closely parallel to that performed in their university roles. It has been estimated that nearly 100% of the top scientists in the biotechnology field are now connected to one company or another.

"Cal Gene", the Allied Corporation and the University of California provide a case in point. Cal Gene, Inc. was co-founded by professor Raymond Valentine, who is also its Vice President. Valentine's research identifying nif genes that allow certain plants to produce their own nitrogen from the air, thereby reducing the need for fertilizer, was potentially of enormous financial benefit to Cal Gene, Inc. Within a matter of days of providing a $2.3 million grant to UC to support this work, Allied Corporation also purchased a 20% interest in Valentine's company at a cost of $2 million. The Allied contract was to fund five co-investigators for five years, one of whom was Valentine. The grant was a large one, roughly equal to the average annual receipt of all other gifts and grants made in support of UC agricultural research combined.

As these facts became known, a reaction occurred both within and outside the University. Cocnern was expressed by numerous faculty members in a series of internal letters, submitted separately to the Subcommittee. One such letter signed by most members of the bacteriology department indicated their view "that involvement of experiment station members in [Cal Gene] constitutes a clear conflict of interest". Equally disturbing were several reports from graduate students that they were unable to satisfactorily complete their graduate research because of the relationship between the Valentine lab at UC and Cal Gene. A memorandum from a distinguished member of the UC faculty, Dr. Emanuel Epstein to Dean Charles Hess, touched the heart of the matter. In it, he stated:

> Charlie, one aspect that I believe to be exceedingly important was not included in the discussion of this matter by the College Faculty on Tuesday, November 24.
>
> Occasional consulting and other relatively minor extramural activities are often beneficial all around, but long-term commitments involving substantial financial interest are something entirely different, and particularly so if the extramural entity is a business run for profit. The damage such involvement may cause--is already causing on our campus--is this: the vital ingredient of academe, free and mutually stimulating exchange of information and ideas, is stifled.
>
> In the past it was the most natural thing in the world for colleagues to swap ideas on the spur of the moment, to share the latest findings hot off the scintillation counter or the electrophoresis cell, to show each other early drafts of papers, and in other such ways to act as "companions in zealous research."
>
> No more. Any U.C.D. scientist with a promising new slant for the improvement of nitrogen fixation or the enhancement of salt tolerance of crops or accelerated in vitro culture of plant tissue will think twice before talking about it to anyone who is connected with either of the two Davis crop genetic private enterprises--or even with colleagues who in turn might speak to any such person. I know that this type of inhibition is already at work on this campus.

> In addition, graduate students of faculty members connected with these businesses are in danger of being directed in ways more tailored to the requirements of those enterprises than the students' educational and professional advancement.
>
> It should be made clear to University people associating themselves with businesses of this kind that in so doing they may cut themselves off from the essential spontaneous, free flow of information and ideas that is the very lifeblood of the academic enterprise, and that the integrity of their direction of graduate students may no longer be unquestioned.
>
> No matter what formal policies are promulgated, conscientious University scientists will take what measures they individually can to protect their own, the University's, and the public's right to their ideas and findings, and to safeguard the rights of graduate students. As a result we have this new guardedness, caution and suspicion.
>
> I therefore have my doubts about any very "positive" approach to this development. I feel that in any statement on this problem by the University the inevitable damage to the academic enterprise that I have discussed here should be clearly spelled out. In effect, what this intimate connection of some of our faculty with corporate business is doing amounts to no less than an insidious but nonetheless real abridgment of the academic freedom of all members of our college and their graduate students. That, I believe, is the main issue that must be confronted.

In addition, the facts of the Cal Gene case were made part of a petition filed with the California Fair Political Practices Commission urging that the Commission adopt regulations making the state's conflict of interest laws applicable to the University of California faculty. Other potential conflicts at UC were identified, including the involvement of professor Herbert Boyer with Genetech, which other UC faculty members stated was actually started in a UC laboratory. Questions were also raised about participation of several UC faculty members in a joint venture known as "Engenics."

Faced with this increasing criticism, Ray Valentine was told by the University to either sever his relationship with Cal Gene or relinquish his position on the Allied funded project to support his work on nitrogen fixing (nif) genes. He chose the latter. (However, according to press reports, up to thirty other UC Davis faculty members continue to consult for Cal Gene.) A few days later, The Fair Political Practices Commission voted to issue regulations applying the state's Political Reform Act to University research decisions. Subsequently, in March of this year, the Commission by a 4-1 vote adopted final regulations requiring, among other things, full disclosure by UC scientists of any financial or equity interest they may have in business entities funding their research, through gifts, grants or contracts. Rules were also approved requiring such faculty members to delegate to a committee any decisions on research where such a potential conflict was present.

(2) The Response of Academia to the Commercialization of Research

During last year's Subcommittee hearings, in response to a question from Congresswoman Heckler, Stanford President Donald Kennedy acknowledged that commercialization of University research was proceeding "at a gallop" but expressed the hope that universities could move rapidly to address the emerging ethical issues involved. That hope, unfortunately, has thus far remained unfulfilled.

The primary response by major universities to the variety of policy issues presented by commercialization of research, in biotechnology and in several other fields, has been a conference convened in March at the secluded California retreat of Pajaro

Dunes.

Its purpose was to establish ground rules for the relationship between universities and private corporations in performing commercial research on campus.

Participants included the presidents of Harvard, Massachusetts Institute of Technology, Stanford, the University of California and California Institute of Technology. Also included were the chief executives of 11 high-tech corporations in biotechnology, including Du Pont, Eli Lilly and Genetech. Finally, hand-picked members of the faculties of these schools also were present chosen principally for their previous connections to commercial concerns, as directors, investors or consultants.

How decisions are made on the disposition of hundreds of millions of public research dollars from federal and state governments was at stake at this meeting. But the public was not invited. Members of the press were notified that they were not welcome. Neither were environmentalists, health-care specialists, consumer representatives or labor officials.

More significant than the comparatively narrow makeup of the Pajaro Dunes conference was the paucity of its result. The document produced by the conferees consisted only of the vaguest of guidelines. Moreover, it failed to address the vital issues surrounding conflicts of interests or the use of exclusive patents provided to business entities contributing to university research projects. The Washington Post in an editorial summed up the results this way:

> What the five university presidents produced last weekend doesn't really get to the problems. It is largely a statement of unexceptionable general principles, combined with hortatory language on the need to preserve "basic academic values" and so forth. It winds up, disappointingly, as "an agenda of issues" not of "attempted" answers. Perhaps that was inevitable, considering the narrowness of the group. But the effort shouldn't stop here. Universities, and science as a whole, would benefit from an attempt to hammer out rules to guide the development of new relationships with business that won't endanger academic science. Washington Post, April 5, 1982.

During the past several years, I have kept rather close tabs on university attempts to deal internally with conflicts of interest issues. They have been singularly unimpressive. An attempt last year, for example, at Stanford to adopt a modest conflict of interest proposal was voted down resoundingly by its faculty. Likewise, the University of California unsuccessfully fought disclosure requirements under state law, both for its faculty and the members of its Board of Regents, for nearly eight years. I am unaware of a single research university in the United States that requires simple disclosure by its faculty of interests in business entities potentially benefitting from their research efforts, although those efforts are supported overwhelmingly with public funds.

(3) The Need for Federal Guidance

As Donald Kennedy noted in his testimony, the "commercialization of university research may bring substantial benefits, such as new funding and increased technology transfer, but also is fraught with dangers." These include what Dr. Kennedy characterized as "the prospect of significant contamination of the University's basic research enterprise by the introduction of

strong commercial motiviations and potential conflicts of interest on the part of faculty members with respect to their obligations to the corporations in which they have consultancies or equity and then obligation to the university." Another perhaps even more important danger, not mentioned by Dr. Kennedy is the real potential that in allocating research funds it allows the commercial potential of new technology to overwhelm other considerations, such as its impact on the society at large. In other words, the introduction of commercial motivations and self interest may have a direct impact on "what questions are asked" at universities when research direction is set. Fear of this result was eloquently noted by President Eisenhower in his Farewell Address, where he said:

> The prospect of domination of the nation's scholars by Federal employment project allocations, and the power of money is ever present--and is gravely to be regarded.
>
> Yet, in holding scientific research and discovery in respect, as we should, we must also be alert to the equal and opposite danger that public policy could itself become the captive of a scientific-technological elite.
>
> It is the task of statesmanship to mold, to balance, and to integrate these and other forces, new and old, within the principles of our democratic system--ever aiming toward the supreme goals of our free society.

Many of the policy issues involved here are highly complex. What should be the public's return for funding basic research now of potential commercial benefit? Should exclusive patent licenses be providing to corporate sponsors of research? Should scientists be disqualified from participating in publically funded research because of a direct financial interest in the result?

These and other issues require further study. However, one important first step can and should be taken now, and will be only with federal guidance. That step is requiring public disclosure by university scientists accepting federal research funds of their financial interest in business firms or other sources of income which foreseeably will benefit from the research effort. Such a financial interest can take several forms: an equity interest in a private genetic engineering firm, a position on a corporation's board of directors, or the receipt of significant consulting income. The "California model" referred to above required such disclosure of interests in research sponsors. But that only applies to state universities in California and also does not reach interests in business entities benefitting from tax financed research but not actually sponsoring it.

Without some incentive from Congress, it is extremely unlikely that universities will voluntarily take this important step. Yet the public has a right to know that decisions on research priorities are being made in the public interest of society, not the private interest of the scientist involved. The Subcommittee should therefore consider recommending legislation conditioning the receipt of federal research funds by universities on the adoption of a Code of Ethics having as one of its key provisions a requirement of financial disclosure. Such provisions are now in effect for state and federal government officials, legislators and judges among others. Nothing less should be expected of those individuals in positions of trust who chcose the direction of new technology, and with it, the future characteristics of our civilization as a whole.

Mr. GORE. Next we will hear from Dr. Charles Hess, dean of the College of Agriculture and Environmental Sciences at the University of California at Davis.

Please begin your statement, but let me warn you that we have a vote on the floor and very shortly I will be constrained to interrupt and we will take a brief recess for the vote.

Go ahead and get started.

Dr. HESS. Thank you, Mr. Gore.

I believe that the House Committee on Science and Technology and the subcommittees have chosen a good case study for university-industry relations. I would like to describe the relationships at University of California-Davis between Calgene-Allied Chemical, the complications which developed from those relations, and then the short- and long-term solutions for what we viewed as potential conflict-of-interest situations.

The story begins with a very active program on the Davis campus in biological nitrogen fixation. This is the process by which soil bacteria invade the roots of plants in the pea family, such as soybeans, alfalfa, and stimulate nodules. The bacteria live in the nodules and get sugars from the plant and reproduce. But it is not a one-way street. The bacteria can take nitrogen from the atmosphere in the soil, convert it to ammonia and release it to the plants for their nitrogen source.

In other words, the plants have their own nitrogen fertilizer factory in their root system. We are interested in seeing if this biological process can be expanded to other plants, as was referred to in earlier testimony, such as nitrogen-fixing corn or wheat. This would have tremendous implications on productivity, reduce our dependency on foreign nitrogen sources and so forth.

Prof. Ray Valentine at University of California-Davis has been active in this field for some time, and has identified the gene in the rhizobia bacteria which gives it its nitrogen-fixing ability, and he has transferred that gene from one bacteria to another. One long-range goal is to try to transfer that ability to other plants.

In 1977 the National Science Foundation gave the college a unique 5 year, $3.9 million grant to support the work in this area. It was given under the NSF–RANN program, Research Applied to National Needs.

During the period of the grant there were numbers of reorganizations that were taking place in applied research in NSF and the funding for applied research was cut back in the foundation. So by 1980, Valentine and others began looking for alternative funding sources. One approach that Valentine suggested was to set up outside of the University of California structure an organization which could receive funds from the industry and which could generate additional funds from patent royalties.

Mr. GORE. If you will excuse me, we will pick up the story at the point you began looking for money.

[Recess.]

Mr. GORE. The subcommittees will come to back into session.

Dr. Hess, please proceed. I think, incidentally, that is likely to be the last interruption before the conclusion of the hearing. I hope so.

Dr. HESS. We were looking for alternative sources of funding. However, the concept of some sort of a private venture associated outside the university structure, but sanctioned by the university, was not viewed with any support.

At this time industry was becoming interested in genetic engineering of the type we were doing, and were interested in establishing a window into this new technology. They may not have the capability to conduct the research with their in-house research staff, but they wanted to see what was going on, which then could help in decisionmaking as to whether to pursue that area internally.

Both Ray Valentine and I contacted a number of firms including Allied Chemical to see if they would have an interest in supporting the research we were doing. Negotiations were initiated with Allied, both on a scientific and on a contractual basis.

One point I would like to emphasize here is that we went to industry with proposals of research that we were interested in doing. We wanted to further our knowledge in enhancing plant productivity, particularly in the area of biological nitrogen fixation.

Meanwhile, Professor Valentine being a very active individual, was exploring other possibilities to provide sustained funding for his laboratory. Specifically that was the concept of establishing a private genetic engineering laboratory in Davis which could attract venture capital, industry support, and so forth. In November 1980, papers were filed with the California Secretary of State incorporating Calgene.

The concerns about the establishment of Calgene and the involvement of some of our faculty from the Davis campus as well as other University of California campuses on the Calgene Science Board, began to grow during the winter and spring of 1981. And in response to this concern, and to provide a forum to discuss the issues, we held a town meeting with the faculty on May 25, 1981. We had a number of speakers, including members of the Calgene Board, who were on our faculty, department chairs, the dean of the graduate school, and myself.

In the discussion the advantages of university-private relations were pointed out: One, a funding source; two, attracting other scientists in genetic engineering from other universities or from industry to come to the Davis campus, as well as work with Calgene and give seminars on campus; three, the potential of retention of faculty who might otherwise be attracted to private sector; four, job opportunities for graduate students and post-doctorates: and five, a more rapid transfer of knowledge, basic knowledge, to application.

But there were also clearly a number of disadvantages which were seen: One, the reduction of informal intellectual commerce, or the discussion of ideas; two, the potential of conflict of interest; three, misdirection of graduate students; four, too much emphasis on applied research, which would take scientists who had been doing basic work in genetic engineering, gene expression, gene transfer, and now concentrate on the development of products that could be marketable in order to meet the obligations to the investors, and therefore be forced into looking at product-oriented research.

On the basis of this town meeting, my own feelings were that the disadvantages outweighed the advantages. We began the development of a new policy to supplement existing policy in the college, and the experiment station, which required prior approval of faculty before they became engaged in consultation. The criteria for whether or not we would allow a faculty member to consult externally was that that consultation would be beneficial to their research and teaching, it would be done on their own time, on vacation time, and that any university resources that were used in connection with that consultation would be reimbursed.

So at this point we had the situation where National Science Foundation funding was decreasing, Allied had been contacted, Calgene had been formed, the faculty were really beginning to get concerned about university-industry relations, and we were in the process of developing a new policy.

In the meantime, the negotiations with Allied Chemical were finally completed and the university general counsel and the patent office signed off on a contract. The contract was for a 5-year period, to conduct research that will increase knowledge in the enhancement of plant productivity and energy and nutrient use efficiency.

There were four major research objectives and five faculty involved, including Ray Valentine. Total funding for the 5-year project was $2.512 million. That amounts to about $500,000 a year, or about 1.5 percent of our research budget. All direct and indirect costs were paid by Allied Chemical. And the equipment that was purchased under the grant or contract would become property of the University of California.

There was freedom to publish, much like what was described earlier, to insure freedom of exchange of information. Formal publication required a 30-day notice for the sole reason of protecting patent rights. The patents belong to the University of California, and Allied had the right of first refusal to obtain exclusive royalty-bearing licenses and they had 90 days to decide whether they wished to do that. If not, the university could pursue those patents and the licensing of them at their interest.

It was also in the contract that licenses shall be subject to diligent commercial development so that they would not be tied up and restricted from public use.

After the contract was signed on June 28, 1981, an article appeared in the local and San Francisco papers on July 9 announcing the purchase of a 20-percent interest in Calgene by Allied Chemical. Although there was no evidence of a conflict of interest, the faculty and the public perception of, or the potential for a conflict of interest was so great in my opinion that some action was necessary.

I offered Professor Valentine three options. One, was to disassociate himself from Calgene. Two, was not to be on the Allied contract. And three, was to not be a member of the Agriculture Experiment Station, and become a regular 9-month faculty member like faculty in the College of Engineering or the College of Letters and Science. Ray chose not to be on the contract. I notified Allied that we would not be able to do the research under Ray's portion of the contract. That was a million-dollar decision essentially—of the

$2.5 million contract, $1 million would have supported Ray's research.

At the time when this decision was announced, the students in Ray's laboratory became concerned, because they had realized that funding from the Allied contract would probably be an important source of their assistantships and research support. They came to me to say "What is going to happen to us." My response was that this is an administrative decision, and therefore we will assure that you will be able to continue your graduate studies.

Also, by this time the issue of faculty involvement in private laboratories in which individual faculty members had an equity interest was highly controversial, and a number of the students in Valentine's laboratory decided they wanted to relocate. The controversy was just too much hassle, and it was interfering with their research and studies. The faculty in the bacteriology graduate group helped to relocate the students and we provided support for them to continue their research.

There was one student in Valentine's laboratory who Ray approached and offered support from a grant in another area of research Ray stated, if you would like to change your research, I can provide you with funding so you can continue to work in the laboratory. And the student came to me and said:

> I would like to work with Valentine, it is an exciting place to work, but I would really like to continue my graduate studies in the research area that I have already initiated so I can complete my studies more expeditiously.

So we then arranged for that student to change to another department and provided support for his research and assistantship. Some people have used this case as an example of where the student's research was being modified to fit the interests of Calgene. I don't believe that was the case. The case was that Ray had alternative funding from within the university, to do university research, not to benefit the interests of Calgene.

However, I also will readily admit that that potential for this type of conflict of interest certainly does exist, and it is an area that we have a lot of concern about.

The Davis campus was not the only unit within the university that had concern about the industry university interactions. President Saxon appointed a systemwide committee on the rights to intellectual property to assess "new and unusual problems raised for the university by the recent innovations in genetic engineering." The committee report is now in almost final form.

Some members of the committee felt that faculty should not normally serve as principals or hold line positions in outside firms, except those unrelated to their professional service to the university. In other words, if they were a biochemical engineer and they wanted to consult for some kind of an equipment company, whose research was completely different, but the faculty's expertise was needed for some reason, that would be OK. But if they were doing biochemical engineering in the outside firm, and it was the same research they were doing in the university that would not be acceptable.

The majority of the committee also believed that contracts and grants should not be accepted from outside entities to support fac-

ulty research if the faculty member involved holds substantial stock or equivalent interest in the entity offering the grant or contract.

Now, based on experience that we have had with the Valentine, Calgene-Allied relationship, and committee reports, such as on intellectual property, we have modified the college consulting policy that I described earlier, and as of June 1 this year, we require full disclosure of any financial interest in firms with which an individual proposes to consult or develop some type of a formal relationship.

As Mr. Meyerhoff has pointed out, faculty also have to disclose to the Fair Political Practices Commission any financial interests that they have in a nongovernmental agency from which they propose to receive a contract or grant. The information that is reported on our modified consulting agreement will be reviewed first at the departmental level by the chair who will recommend approval or disapprove of that agreement.

We feel it is important to have review at the local level by individuals who are most closely associated with the faculty. The dean receives and reviews the consulting forms material and makes a decision to approve or disapprove the proposed activity and informs the faculty member and the department chair.

I feel there are many benefits from university/industry relationships. It insures relevance of research, the more rapid application of new knowledge to solve society's problems, like productivity, and it can provide a source of funds to support the university research.

Land-grant colleges have had a long history of close working relationships with the private sector. Congress in 1864, as Mr. Weber was pointing out, helped provide the link between research, teaching, and the private sector by establishing land-grant colleges.

The major problem in the current situation is that of faculty trying to operate in both the university and the private sector at the same time. It is a situation that causes the greatest concern, and it has the greatest potential for conflicts of interest. There may be cases where dual relationships are beneficial. Most cases produce a potential conflict of interest that is not acceptable.

We believe the disclosure policy we have developed will provide a mechanism to determine what is acceptable and what is not. In this way I think society can have the benefits of the university-industry relationships without the drawbacks.

The bottom line is that we have been responsive to the challenges that have been put before us by the interactions between the university and the private sector. We have worked for solutions carefully, not wanting to overreact and create policy which was in the disinterest of the university, the faculty or the public. It is my preference that the university provide guidelines for its actions, rather than having them legislated, either by State or Federal Government.

[The prepared statement of Dr. Hess follows:]

THE EVOLUTION OF CALGENE, A POTENTIAL CONFLICT OF INTEREST AND ITS RESOLUTION --FROM A DEAN'S PERSPECTIVE*

The evolution of Calgene and the subsequent interactions among faculty and the private sector is a story of faculty searching for alternative ways to fund an important area of research in the face of declining federal support. The area of research in this example is biological nitrogen fixation.

Plants of the legume or pea family form nodules on their roots in response to the invasion of soil bacteria known as rhizobium. The bacteria live and multiply in the nodules and are supplied with sugars by the plant. The bacteria in turn have the unique ability to take nitrogen from the air, fix it into ammonia, and then release it to the plant. Under these conditions, the plant has its own nitrogen fertilizer factory incorporated into its root system.

Professor Ray Valentine of the UC Davis campus has identified the gene which gives rhizobia bacteria the ability to fix nitrogen and has transferred that gene from one bacteria to another. A long-range goal is to transfer that genetic information to other plants such as wheat, corn or rice so that they, too, could become nitrogen fixers.

Research in biological nitrogen fixation is of intense interest at Davis and other university campuses because nitrogen fertilizers are manufactured from natural gas in a high energy-requiring process. The ability to biologically fix nitrogen would reduce our dependency upon an expensive nonrenewable resource. Also, since the nitrogen would be made within the plant that was using it, the potential of introducing nitrogen fertilizers into the ground water would be reduced.

Research in biological nitrogen fixation was initially funded by a National Science Foundation grant which provided a $3.9 million grant to faculty members

*Testimony presented by Charles E. Hess, Dean of the College of Agricultural and Environmental Sciences, University of California, Davis, California. Presented to the House Committee on Science and Technology, jointly sponsored by the Subcommittee on Investigations and Oversight and the Subcommittee on Science, Research and Technology, on June 16, 1982, Washington, D.C.

on the UC Davis campus for a five-year period. Professor Ray Valentine was one of the principal investigators on the grant. The grant was set up for a five-year period to provide a sustained research program under the auspices of the NSF RANN (Research Applied to National Needs) program. The applied research programs of the Foundation were reorganized a couple of times during this period and by 1980 it was clear that support for research in this area by the Foundation was being cut back.

At this point, Professor Valentine proposed the idea of setting up an entity outside of the normal University of California structure which could receive funds from industry and provide sustained support for research. It also was suggested that patentable discoveries could generate royalties which would be channeled back into the research program which generated the discovery. However, there was no encouragement from the Davis campus to establish a unit outside of the normal University structure. Mechanisms already existed to receive grants or contracts from the private sector and the University has a policy that patents will remain the property of the University and part of the royalties go into The Regents Opportunity Funds.

Professor Valentine's concern for sustained funding of this important research program remained and, therefore, other alternatives were explored. At this time, a number of firms were beginning to become interested in the potential for genetic engineering research and a number of companies were contacted to determine their interest in funding a program in biological nitrogen fixation. Allied Chemical was one of those firms. It expressed an interest in contracting for research in biological nitrogen fixation and other areas of mutual interest. Negotiations were initiated among scientists and lawyers to develop a research plan and a contract.

Meanwhile, Professor Valentine explored also the possibility of establishing a private research laboratory which could attract support from industry or from venture capital. On November 5, 1980, papers were filed incorporating Calgene. Word about the formation of Calgene and the involvement of several faculty

members from UC Davis and other universities on a science advisory board spread through the Davis campus, raising questions about the advantages and disadvantages of these relationships. In response to this concern and to provide a forum to discuss the issues, a town meeting was held on the UC Davis campus on May 25, 1981.

The advantages included the potential funding of both basic and applied research, the attraction of outstanding scientists to the Davis campus, the possibility of retaining outstanding faculty who might otherwise be attracted away to other private ventures, and possible job opportunities for graduate and postdoctoral students. On the negative side of the ledger was the creation of a real or a perceived conflict of interest on the part of faculty who were operating both within the University and in a private venture. Secondly, there was a concern that the direction of graduate students' research programs might be channeled to benefit the interests of a private research venture, possibly at the expense of the students' graduate program. Third was the possibility that outstanding scientists who had up to now been conducting fundamental research in gene transfer and gene expression would now turn their interests to highly applied product-oriented research in order to return a profit to the investors who funded their company.

Although a consensus was not determined at the meeting, my own feelings were that the costs of faculty involvement in private research ventures similar to their University research outweighed the benefits. Therefore, we began to develop policy and guidelines for faculty as they considered a financial involvement in private research laboratories whose research was the same as their University research. It should be pointed out that the College of Agricultural and Environmental Sciences at UC Davis already had policy regarding consulting which was more restrictive than other units on the campus. The reason for a more restrictive policy is that members of the faculty are also members of the California Agricultural Experiment Station and hold 11-month or full-time positions. In contrast, other members of the faculty in the UC Davis College of Letters and Science or College of Engineering, for example, have nine-month appointments and are free in the summer to consult or secure employment through grants, etc. Our policy required faculty to obtain prior permission before becoming involved in an outside consulting activity.

The criteria used for approving such an activity include determining whether the consulting activity enhances the faculty member's teaching and research programs, whether the consulting activities are conducted on personal time, and whether and how the University would be reimbursed if University facilities were to be used. Although this policy was in effect since 1975, it was felt that the new involvement of faculty in private research ventures in which they had a financial interest posed special problems and required the development of new policy or guidelines.

In the meantime, negotiations with outside firms for research support had continued and a contract between Allied Chemical and the University of California was developed to support research in biological nitrogen fixation and in other areas. There was an extended period of negotiation because the patent office wished to be sure that the University's interests were adequately protected. The contract provided that any patents which might result from the research would belong to the University of California, but since Allied was prepared to pay for all costs of the research, it would be given exclusive licensing rights to any resulting patents. Negotiations were completed on June 28, 1981 and a contract was signed.

After the signing of the contract, an article appeared on July 9th in the local papers which reported that Allied Chemical had purchased a 20 percent interest in Calgene. Although there was no proven conflict of interest between the Allied contract and Professor Valentine's involvement in it, and Allied's subsequent purchase of an interest in Calgene, I believed that the public perception of or the potential for a conflict of interest was so great that action by my office was required. On August 3, 1981 I offered to Professor Valentine three options: one, disassociate himself from Calgene; two, not be a principal co-investigator on the Allied grant; and three, to resign from the portion of his position in the Experiment Station. Professor Valentine then notified me that he would not be a co-investigator on the Allied grant. We notified Allied Chemical that we would not be able to conduct the research in that portion of the contract developed by Professor Valentine but that other components of the research could be continued. Subsequently, Professor Valentine also submitted his resignation as a member of the Experiment Station. However, since he was no longer working on the Allied grant, I felt that the strong conflict of

interest potential had been removed. I did not accept his resignation from the Experiment Station, for I believed that it was in his and the University's interest not to reduce his research time. His portion of the contract represented $1 million of the $2.5 million grant.

When the decision was made not to conduct the research in Professor Valentine's section of the contract, I met with some of his graduate students who were concerned about what their future source of support might be because they had relied on continued support from the Allied contract. I told them that since it was an administrative decision not to conduct Professor Valentine's portion of the Allied grant, we would work with them to provide research support and, if necessary, relocate their programs.

By this time, the issue of faculty involvement in outside laboratories in which they had an equity interest was very controversial. Some students indicated that they wished not to remain in Professor Valentine's laboratory. Faculty from the Bacteriology Graduate Group helped find other faculty who would be willing to accept Professor Valentine's students and in a number of cases we did provide support to allow them to continue their research. In one case, Professor Valentine offered a student the opportunity to change his research program and to be supported from another grant which Professor Valentine had. However, the student would have to change his research program. The student said that although he would like to work with Professor Valentine, he would prefer to carry on the research that he had started so that it would not delay the completion of his degree program. We honored the student's preference and arranged for him to move to another department and to continue his same line of research. Some people interpreted this event as evidence that a student's research program was being redirected to meet the needs of Calgene. I believe that such was not the case. Instead it was as I described -- an opportunity to be funded from another research grant in an area different from the student's initial research and having no relationship to Calgene research programs.

Subsequent to our decision not to conduct the research in the Valentine portion of the Allied contract, the California Rural Legal Assistance (CRLA) and Mr. Paul Barnett filed a "comment" with the California Fair Political Practices

Commission urging it to reconsider the blanket exemption of University of California faculty from the disclosure and conflict of interest provisions of the Fair Political Practices Act. The Fair Political Practices Act requires state employees to disclose outside financial interests which could create a conflict of interest in the conduct of their official duties. Nine alleged "case studies" were presented to illustrate possible conflict of interest situations. The "case" of Professor Valentine and his involvement with Calgene and Allied Chemical was included in the CRLA presentation. The Fair Political Practices Commission did reconsider the exemption given to UC faculty, held a hearing, and ruled on March 1, 1982, that it would not remove the exemption but required that principal investigators on a contract or grant from a nongovernmental entity must disclose any financial interest they have in that nongovernmental entity.

The UC Davis campus was not the only unit concerned about university-private sector interactions. President David S. Saxon appointed a systemwide committee on Rights to Intellectual Property to "assess new and unusual problems raised for the University by recent innovations in genetic engineering." The draft report, circulated this March, is an excellent analysis of the issues. Some members of the committee suggested that faculty members should not normally serve as "principals" or hold line positions in outside firms except those unrelated to their professional service to the University. A majority of the committee believed that contracts or grants should not be accepted from outside entities to support faculty research if the faculty involved held substantial stock or equivalent interest in the entity offering the grant or contract.

Based on our experience in dealing with the Valentine-Calgene-Allied relationships, on our 1975 consulting policy and the reports of committees such as the Rights to Intellectual Property, we have modified our original consulting policy. Effective June 1, 1982, we require full disclosure of any financial interest in firms with which an individual proposes to consult or develop a formal relationship. The information is reviewed by the departmental chair who recommends approval or disapproval of the proposed activity to the dean. The dean then reviews the proposal for outside professional activity and notifies the faculty member if the proposed activity is approved or disapproved.

We believe that the modified policy on outside professional activities will provide the information necessary to judge whether the proposed activities are in the best interest of the University, the public, and the individual, and whether a potential conflict of interest does exist. (A copy of the letter to the faculty and staff and form used to apply for prior approval for outside professional activities is attached.)

In closing, I feel that university-industry interactions are critically important. As Denis Prager, Assistant Director of the Office of Science and Technology Policy, wrote in the January 1980 issue of SCIENCE, good university-industry relations help insure that research is relevant to national needs and bring about a more rapid application of new knowledge to solve societal problems, thus helping to increase productivity.

Land grant universities such as the University of California at Davis have a long history of a close working relationship with the private sector--agriculture. Congress in 1862, recognizing the importance of a viable agriculture to the nation, endorsed the concept of linking teaching and research with the private sector by establishing land grant colleges. The major problem in the current situation is that of faculty trying to serve (and have a financial interest in) both the university and the private sector at the same time. This is the situation which causes greatest concern and creates the greatest potential for conflicts of interest. In some cases the dual relationship may be beneficial to all parties involved. In most cases it will cause a potential conflict of interest that is not acceptable.

We believe the disclosure policy I have described will provide the mechanism to determine what is acceptable and what is not. In this way society can have the benefits of the university-industry relationship without the drawbacks.

Attachment

DAVIS: COLLEGE OF AGRICULTURAL & ENVIRONMENTAL SCIENCES
AGRICULTURAL EXPERIMENT STATION
OFFICE OF THE DEAN AND ASSOCIATE DIRECTOR

April 30, 1982

FACULTY - COLLEGE OF AGRICULTURAL AND ENVIRONMENTAL SCIENCES
STAFF - DIVISION OF AGRICULTURAL SCIENCES

RE: Outside Professional Activities

As you know, we have been working since last spring on guidelines and policy for outside professional activities. We have discussed the issues at a Town Hall meeting, at the Fall Faculty and Staff Meeting, and we have reviewed draft statements with the Research Policy Committee, the Executive Committee, and with the Experiment Station Council of Directors. In the meantime, a Campus ad hoc Committee on Conflicts of Interest and two Systemwide Committees studied the challenges which face the faculty and the University caused by the great interest of investors to become involved in the new biotechnology of genetic engineering. All three committees -- the ad hoc Committee on Conflicts of Interest, the University-Industry Relations Project, and the Committee on Rights to Intellectual Property -- have issued draft reports. Also during this time, the University and the Fair Political Practices Commission issued a new policy that requires faculty who negotiate contracts with nongovernmental entities in which they or their immediate family have a financial interest to disclose the nature of that interest.

Based on reports mentioned above, from discussions with our College committees and from letters you have sent to me, a general consensus has been expressed that 1) faculty members should not have a financial interest or serve in a decision-making position in outside firms directly related to their professional service to the University and 2) that contracts or grants should not be accepted from outside firms in which a faculty member has a financial interest or serves as a paid consultant.

However, based upon the experience of the past year, I do not feel it is possible to develop a single policy that could take into account all the possible circumstances and variations that arise in University-private sector interactions. Therefore, in order to be fair to all parties -- the individual, the public, the University, and the private sector -- I feel the solution is to require full disclosure of any financial interest in firms with which an individual proposes to consult or develop some formal relationship. This information can be reviewed first by the Department Chair who would recommend approval or disapproval of the proposed activity to the Dean. The Dean will notify the faculty member through the Department Chair of the decision on the proposed activity.

UNIVERSITY OF CALIFORNIA - (Letterhead for Interdepartmental Use) D3250

To implement the policy of disclosure, we will continue with existing Experiment Station policy on consulting and add to it a request for information about financial interests in the firm with which a consultantship is proposed. Disclosure of financial interests in regard to contracts and grants will be handled through the procedures being developed by the University in compliance with the rulings by the Fair Political Practices Commission.

The attached statement will be incorporated into the College's Research Manual and will be given to new faculty when they are employed. The attached form will be used starting June 1, 1982.

Charley

Charles E. Hess
Dean

CEH/lh
Attachments

OUTSIDE PROFESSIONAL ACTIVITIES

The University of California recognizes that involvement in outside professional activities benefits the individual and the University through expansion of knowledge and experience which can be applied to teaching, research, and public service.

The basic authority for Division of Agricultural Sciences' policies can be found in The Regents Standing Order 103. A variety of specialized policies and guidelines also have been issued. These are summarized in the "Compendium of Specialized University Policies, Guidelines, and Regulations Related to Conflict of Interest," Office of the President, June 23, 1980.

Because of special circumstances and privileges surrounding obligations involved in the 11-month responsibility associated with an Agricultural Experiment Station appointment, Vice President Kendrick issued the April 30, 1975, policy statement of the Division requiring prior approval by ". . . the cognizant Dean, Director, Associate or Assistant Director" in order to engage in any consulting activity involving additional financial compensation. "Consulting" is interpreted to mean the provision of professional, managerial, or technical services to clients, private firms, nonprofit organizations, or any governmental agencies.

So that any proposed consulting activity's merits may be evaluated, a full disclosure concerning the activity, including any financial interest in the firm or agency involved, must be provided. This statement should disclose any income, investment, or management position in the firm or agency received in return for the proposed activity.

The attached form is intended to facilitate applying for permission to engage in outside consulting activities. Such requests will be prepared by the individual and be forwarded to the Dean with the Department Chair's recommendation. The Dean will notify the faculty member through the Department Chair of the decision on the proposed activity.

4/30/82

99-177 O - 82 - 6

REQUEST TO ENGAGE IN OUTSIDE CONSULTING SERVICE
INVOLVING ADDITIONAL FINANCIAL COMPENSATION

NAME_____ DATE_____

DEPARTMENT_____

The policy of the Division of Agricultural Sciences requires prior approval by the Dean for each consulting commitment (Division of Agricultural Sciences' policy, April 30, 1975). Approval to engage in the proposed activity will be given for a one-year period and renewal will be based on reapplication.

ACTIVITY

1. Name and Address of agency or firm:

2. Description of the activity including how involvement will provide experience and knowledge useful for your teaching and research and how you are able to make a contribution to knowledge by engaging in the activity:

3. Consultation, where additional financial compensation is involved (as against providing similar services as a part of the normal public or professional service), is limited to times when you are not in a duty status (i.e., weekends, vacations, or leave without pay). Please provide an estimate of the time devoted to the activity including number of days per month and the length of time that level of commitment will continue:

4. Description of the financial interest to the extent of whether income or investments are received in consideration of the service and whether you are a director, officer, partner, trustee, or hold any decision-making position in the business entity related to the proposed activity.

5. Will University facilities, supplies, or equipment be used? Yes_____ No_____
If yes, describe in detail.

Additional information you feel necessary to provide adequate documentation and support for your request can be provided on additional pages.

_____
APPLICANT'S SIGNATURE DATE

DEPARTMENT CHAIR'S RECOMMENDATION:

APPROVE_____ DISAPPROVE_____

_____
DEPARTMENT CHAIR DATE

DEAN'S ACTION:

APPROVE_____ DISAPPROVE_____

_____
DEAN/ASSOCIATE DIRECTOR DATE

D.O.-A&ES-4/30/82

Mr. GORE. Thank you, Dr. Hess.

I found the statement at the end of your next to last paragraph very interesting because of the experience that you have had in your institution. In discussing the dual relationship that some professors have with universities and corporations, you say, and I quote "in most cases it will cause a potential conflict of interest that is not acceptable." That is a pretty strong statement. I take it that that arises from the experience that you have had.

Dr. HESS. Yes.

Mr. GORE. You also mentioned the graduate students' concerns. One that you did not mention in your prepared statement was that students were required to meet with the company personnel to see if their projects were overlapping with the company's projects.

Dr. HESS. There was an accusation that there was research that was being done by one graduate student in the university that was the same in Calgene. Calgene officials said no, that they were not doing the same research. The purpose of the meeting was to assess whether in fact there was similarity or differences, to assure the student that his work was not being compromisd by efforts in Calgene.

Mr. GORE. But students were required to meet with the company in order to establish whether or not there was an overlap?

Dr. HESS. They were not required to. It was a meeting which was established to try to insure the students and the faculty that there was not an overlap. The concern was that if the research was the same, would the information that the graduate student was developing move into the private laboratory and be used for its benefit at the expense of the student, and the university.

Mr. GORE. But apparently Professor Valentine stated that it was the responsibility of the students and not his responsibility to meet with the company personnel and establish whether or not there was an overlap between the research done at the university and the research done by the company. Why would it be the student's responsibility to do that?

Dr. HESS. That may be Professor Valentine's view. It is not my view that that would be the case.

In fact, we have been working with the Calgene, looking at the possibility of having a team made up of perhaps the dean of the graduate school, myself, and some faculty, to review the projects of Calgene, to assess whether there was overlap or not.

In other words, one of the contentions that Calgene had made in relationship with the Allied contract was that there was no overlap, that is that the research that was being done in the university and that being done at Calgene were completely separate, and therefore there was not a conflict.

The problem is how to assess whether that in fact is the case. And one possibility would be for us to have periodic reviews of the research programs of Calgene, to see exactly what they are doing and how that relates to university research.

Mr. GORE. Well, suppose a student had a research project that had been ongoing for a year or two, and then Calgene became interested in the same research project, and began it, and there was an overlap. Could the student be required to abandon his work as a condition for receiving contingent support?

Dr. HESS. Absolutely not.

Mr. GORE. Has that occurred?

Dr. HESS. To my knowledge that has not occurred.

Mr. GORE. All right, proceed.

Dr. HESS. Let me say the research in this area, biological nitrogen fixation, is being pursued in many laboratories. We have an active program, Du Pont has an active program, Oregon State has a program. And so it is not uncommon for someone to initiate research and have another laboratory also initiate research in a similar area. Some people say that is duplication.

On the other hand, I think this is an area which is of critical importance to agriculture, to society, and if we have more people working on it, and there is a competitive edge, I think that progress will be made much more readily. As you have more minds address the area of research, the better the chance of success.

The American Cancer Society in its support of research is an example.

So that the possibility for a private laboratory to enter into research which is similar to that of a graduate student doing research at the university is very high. But Calgene, let me emphasize, was going out of its way to try and say "Look, we don't overlap, and come and look and see that there is not overlap."

We could not prohibit Calgene from doing research it chooses, and we certainly would not prevent a student from doing that research if Calgene were to initiate it.

Mr. GORE. It seems to me this has a potential to pit graduate students against industry researchers.

Dr. HESS. Again, that is a situation that can exist even if Calgene were not even there. In other words, any of the many genetic engineering firms would like to develop a Rhizobium that would be effective on wheat, for example.

Mr. GORE. But isn't there a much, much greater chance it is going to occur, a likelihood it is going to occur, with the professors involved with the company?

Dr. HESS. Certainly it is more likely that there could be an association with the faculty at Davis, since Calgene is located at Davis.

Mr. GORE. Mr. Meyerhoff?

Mr. MEYERHOFF. I just have a couple of thoughts.

One is that the reason that businesses come to a university, one of the reasons, is that there is an army of graduate students. It is cheap labor essentially. And the relationship between Calgene and the university is not unique. It is perhaps more difficult because the company is directly adjacent to the university. But it is a common problem.

There is a memorandum from a JaRue Manning, graduate adviser at UC-Davis, indicating that four of the five students have transferred out of Valentine's laboratory for two reasons:

First, a statement by Professor Valentine that it is the student's responsibility, and not his, to meet with Calgene personnel and establish the graduate research projects they are working on are not being conducted at Calgene; and

Second is the switching of student research projects as a condition for continued support after students have spent up to 2½ years on a project.

Mr. GORE. Let me identify that for the record and put it into the record.

This is a memorandum dated September 24, 1981, from JaRue Manning, graduate adviser in the Davis Department of Bacteriology, to David Pratt, the chairman of the graduate group in microbiology, which purports to summarize the concerns of the microbiology graduate students, and the two concerns which you referred to are said to be common to all of the graduate students:

First, the statement by Professor Valentine that it is up to the students to go to the company and establish there is not an overlap of projects they are working on, and second, that they would have to switch research projects as a condition to getting continued support.

[The memo mentioned above follows:]

September 24, 1981

TO: DAVID PRATT, Chairman
Graduate Group in Microbiology

FR: JaRue Manning, Graduate Advisor

What follows is an to summarize the concerns of graduate students in the Microbiology Group working in Professor Raymond Valentine's laboratory. These concerns were expressed to me in my capacity as their graduate advisor.

As a result of a number of factors, Professor Valentine has reportedly notified all students in his laboratory that they may transfer their research project to another laboratory if they wish. Four of the five students have expressed the desire to transfer out of Professor Valentine's laboratory. Although each student has concerns that are unique, there are at least two factors common to all of them. First is the statement by Professor Valentine that it is the students responsibility and not his (Professor Valentine's) to meet with CalGene personnel and establish that their graduate research project is not being conducted at CalGene. Second is the switching of student research projects as a condition for continued support after students have spent up to 2 1/2 years on a project. Regarding the second factor, while there is certainly a need to coordinate research activities with objectives stated in grants, etc., the manner in which these changes were made raise a number of questions as to the action taken in these cases.

I suggest that the Executive Committee of the Graduate Group in Microbiology, charged with administration of the graduate program, has a responsibility in insuring that; 1) those students in Professor Valentine's laboratory desiring relocation be relocated if at all possible and; 2) conditions be stated by the Graduate group and agreed to by Professor Valentine that would present a continuation or reoccurance of the present situation. I further suggest that until items 1) and 2) above have been satisfactorily resolved that Professor Valentine not be allowed to accept any graduate students in the Graduate Group in Microbiology.

JSM/la

cc: A. G. Marr

Mr. MEYERHOFF. There are also issues now being raised as to whether graduate students should receive royalties or percentage of royalties for research done in combination with industry. Right now the University of California has a policy whereby 50 percent of all patent royalties from inventions done at the unviersity go to the individual scientist. I think it is the most lucrative formula in the country. Issues are being raised I know at Stanford over whether graduate students should get a piece of the action.

Mr. GORE. If they helped invent the product.

Mr. MEYERHOFF. That is correct.

Mr. GORE. Dr. Hess?

Dr. HESS. I would like to address the two issues that were raised in that Dr. Manning's letter. One, again, I do not agree with Professor Valentine's statement that it is the student's responsibility to find out whether there is duplication or not. I felt that that was something that we should do as an administration in order to try to resolve the question whether there was overlap or not.

In a way, as I say, any private sector could be doing similar research. I think Calgene was trying to go out of their way to assure the students they were not duplicating their research.

The second issue, in regard to the switching research as a condition of continued support, is the example that I described in my testimony. Valentine's research support, $1 million was cut off by my decision. He did have another grant, which was designed to do a specific area of research. He offered one of the students the opportunity of doing work in that new area, if he wanted to continue to work in Valentine's laboratory. He had the choice.

As I said, the student came to me and said, I would prefer to continue on my existing research program so I can finish more quickly. We arranged for the transfer of that student to another faculty member to continue work in that same area, and we provided support.

Mr. GORE. Now, when Calgene was originally set up, were you satisfied that there were adequate safeguards to deal with the real and perceived conflicts of interest?

Dr. HESS. No. That is why we began developing the policies as I have described them and enlarging the consulting policy that already existed in the college and experiment station.

Mr. GORE. Do you think you have now adequately addressed the problem of channeling of graduate students toward commercially attractive research?

Dr. HESS. I guess my own preference would be not to have the Calgene type situation where faculty have dual membership. Our policy is that if the faculty member's research is the same in the university as it is in his or her private laboratory, that we would not approve that type of activity.

I think that the discussions that we have had, the town meetings, the modified policy, have created an awareness on the part of faculty and on the part of graduate students who are here now, and it would be the responsibility of us and the faculty and the administration together to be sure that graudate students are aware of the potential problems that exist with the presence of firms such as Calgene in the town of Davis.

Mr. GORE. Let me point out for the record that Dr. Valentine was invited to testify at these hearings and declined to do so voluntarily. Therefore, his point of view on some of these things is not being given because he chose not to give his point of view, which I think is unfortunate.

Is it true that you have some 30 faculty members that are still affiliated with the Calgene, or serving as consultants?

Dr. HESS. There are four members of our faculty on the Science Board of Calgene, from the College of Agricultural and Environmental Sciences.

Mr. GORE. And how many as consultants?

Dr. HESS. They are the four.

Mr. GORE. Where did the 30 figure come from?

Mr. MEYERHOFF. From a press account—newspaper article indicating there were 30.

Mr. GORE. Are you satisfied that there are only four, Dr. Hess?

Dr. HESS. Yes.

Mr. MEYERHOFF. I should emphasize that such information is hard to come by. Up until very recently, the consultant relationships between the university and the private sector were not a matter of public record. The disclosure accomplished was very, very minimal, not indicating the company for whom consultants worked.

Dr. HESS. That is the disclosure policy for the university. The disclosure policy for the college, however, was different, in which we did require prior approval before a faculty member became involved.

Mr. GORE. The disclosure requirement at Davis only involves the principal investigator, is that correct?

Dr. HESS. No. The disclosure policy we have applied to all faculty in the college and experiment station. Now, there is, as a result of the Fair Politicial Practices Commission reviewing the comments that were submitted by the California Legal Assistance, a change in their rulings in regard to disclosure. They now require faculty who are proposing to receive research support in the form of a grant or contract from a nongovernmental agency to disclose their financial interests, or their family's financial interests, in that now governmental entity.

Mr. GORE. But that is just the principal investigator?

Dr. HESS. That is correct. That is the principal investigator.

Mr. GORE. Do you think that is adequate?

Dr. HESS. No. We as a college do not feel it is adequate.

Mr. GORE. You go further as a college.

Dr. HESS. That is correct. And I believe that the university probably will, too.

Mr. GORE. But currently the university does not?

Dr. HESS. That is right.

Mr. GORE. Currently the university just gets disclosure of the principal investigator.

Dr. HESS. There are two forms of disclosure that the university has. One is a disclosure after the fact. That is, each year a faculty member is to report to the university their outside professional activities, whether they are editors for journals, whether they testify before committees, whether they consult with outside firms.

Personally, I feel that those forms do not contain a lot of information. I certainly agree with Al Meyerhoff on that particular point.

On the Davis campus we have done a good job on insuring that those forms are returned. Other campuses are less active in their insurance that the faculty do report on those forms. But it is after the fact.

Now, the changes that have taken place for our university are before they accept a grant now from an outside nongovernmental agency they have to disclose if they have a financial interest. But that is just for the principal investigator.

Mr. GORE. The Fair Political Practices Commission decision affects only publicly funded universities, is that correct?

Dr. HESS. That is correct.

Mr. GORE. Do you feel that privately funded institutions should be required to have similar disclosure rules?

Dr. HESS. I would not want to speak for private universities. I think that we in the public universities have some special responsibilities, because our primary source of research funds are from the tax dollars. And therefore we have special responsibilities.

Mr. MEYERHOFF. Would you like my views on that, Mr. Chairman?

Mr. GORE. Yes. Although I think I can guess them.

Mr. MEYERHOFF. Just responding to Dean Hess's comments, the overwhelming majority of the funds expended at private universities are public funds. Between 70 and 80 percent of the research funds at the Harvards, MIT's, are public. I don't see any reason for a distinction.

One other point on the FPPC ruling that concerns us: that reaches disclosure only of interests in companies that actually sponsor university research. And I would like to compliment Dean Hess because he has gone a little further than that and required disclosure of interest in companies that could benefit.

The problem with the FPPC approach is that if you have a company like Calgene, and they are in a position to directly benefit from research being done by the university professor, so long as Calgene is not providing funds to the university there is no obligation of any disclosure of an interest to the professor in the company that benefits.

Mr. GORE. Dr. Hess, is it fair to conclude you have kind of had a change of heart on these matters, and that that has come about because of the experiences at your institution that have convinced you that your opposition in the past or maybe downplaying some of these concerns in the past was not correct, and now you have become convinced that these concerns need a higher priority?

Dr. HESS. I don't believe there has been a change of heart. I started out right after our town hall meeting back in May of 1981 when Calgene first started——

Mr. GORE. But Mr. Meyerhoff talked about a battle lasting 8 years.

Dr. HESS. OK.

Mr. GORE. That is not you individually?

Mr. MEYERHOFF. It is not UC-Davis.

Dr. HESS. Actually, what they reflected was that the Regents opposed the disclosure requirement under the fair political practices legislation initially, and they felt that it was an invasion of privacy. So they fought it.

I would say that the university also opposed the modification of the exemption by the Fair Political Practices Commission. And part of that I think comes from the concern that faculty have as they are required to disclose information, what is going to be done with it? They would go back to the 1950's and say information was used or misused during the McCarthy era to persecute individuals because of their affiliation with an organization. I guess that they feel that there is a potential for misuse. So there are some faculty who were opposed to increased disclosure.

Personally, and I think I speak for our college, and I speak, I think, also for the faculty on the Davis campus, we don't agree with that concern, and we feel it is right for the public to know. Also it is correct for the faculty and the students to know if an individual member of the faculty has an outside private interest which is involved in research that is the same as their university research.

Mr. MEYERHOFF. I am sure Members of Congress have felt persecuted at certain times by disclosure of their interest, as have Federal judges.

Mr. GORE. I am sure that is the case.

Dean Hess, did you know that when Allied made their grant that they were also considering making a major acquisition in Calgene?

Dr. HESS. I was not personally aware of that. I knew that Valentine and his business manager, Norma Goldfarb, were exploring numbers of companies for support. So at the time the contract was signed I did not know. I know that representatives from Allied did have a meeting on the Davis campus, and there were discussions about conflicts of interest. They may have felt that there would not be a problem if they became involved with Calgene. But I did not have that information.

Second, I would say that although you would like to be clairvoyant and anticipate all the problems and ramifications of relationships, if I had known about Allied, I am not sure whether I would have said no from the start. But the answer is no, I personally was not aware of it. But once it became public knowledge, I was fully concerned about the implications that it had potential conflict of interest.

Mr. GORE. Mr. Meyerhoff, you referred to the public interest. How do you define the nature of the public interest in basic scientific research?

Mr. MEYERHOFF. I think the main point here is a question of trust. The public relies upon universities for a variety of functions in our society. Those functions include decisions on the direction of new technology, particularly scale specific technology, that is harmful to some segment of the society—robotics, automation, for example. Such vital decisions should not be tainted or influenced by the personal self-interest of the decisionmaker.

Universities also serve as a brain trust in rulemaking by administrative agencies and formulating public policy here in Congress. And to the degree that there is a risk that they become captives of

industry, that brain trust loses much of its credibility. I can mention an example there. Again, I am sorry—it comes from the University of California, the university I am most familiar with.

A scientist named Dr. Charles Hind provides two examples. Dr. Hind performed the toxicological studies at the University of California on a pesticide known as DBCP. At the same time he was a very well-paid consultant for the Shell Oil Co. He determined that this substance caused sterility and cancer in some laboratory animals. He disclosed that information to Shell. It was not made public until several years later. Shell marketed the pesticide, and now dozens of workers in the Lathrop plant in California have turned up sterile. No one knows how many farmworkers will have that condition.

Dr. Hind also testified more recently in a rulemaking proceeding concerning the diminution of lead standards in the workplace, a topic now of some controversy. At the same time he was a consultant for American Smelting, a very well-known lead producer. Such ties have costs, I think. That is why we are pressing for at least as a first step, a code of ethics by universities that will require disclosure, so when a Dr. Hind or any of these other professors make decisions that affect all of us, at least we know a little bit about what their relationship to industry is.

Mr. GORE. So the public interest is, as you express it, an openness and a fairness in having an open decisionmaking process. It is not in judging research priorities, is it?

Mr. MEYERHOFF. No, I don't believe it is, except insofar as—if you have decisions made at policy levels in universities to go in a certain direction, certain kinds of research, and I am thinking here in the toxic area, between chemicals as a form of pest control, for example, and other forms. I think that environmental groups and other organizations that are affected should be aware of ties between those decisionmakers and chemical companies, for example, that may benefit from the use of public funds.

I am a member of a profession that is not held in particularly high esteem as far as trust goes. I think I was 18 before in my family I learned that "shyster lawyer" was two words. So I am concerned that scientists not suffer that same result.

Mr. GORE. That is thoughtful of you.

The public interest can also be served by better technology transfer, can it not?

Mr. MEYERHOFF. Absolutely.

Mr. GORE. And technological innovation.

Mr. MEYERHOFF. But again it is a question of technology transfer to whom and progress for whom. It is not a simple subject.

Dr. HESS. Could I——

Mr. GORE. Yes, I would like to ask you to comment.

Dr. HESS. I was interested in Al's hesitation as to whether disclosure would affect research decisions, research priorities or not, because I think in part there is a bit of a danger, and it goes back to the question of disclosure for what.

If it is disclosure to know where an individual is coming from when they are testifying or advising and so forth, that is fine. I think it is a situation that can be easily controlled. As a person is asked to testify, you can ask what are your affiliations. If you are

testing on the use of a pesticide, do you have an affiliation with a chemical company that manufactures that pesticide?

On the other hand, if the purpose of disclousre is to say we don't want that individual to decide to do research in pesticides, or in a topic we have been involved with for years now, mechanization, it is another case. Al feels that mechanization research is to the disadvantage of farmworkers, he sees it as a displacement of jobs.

I can look at mechanization another way. I can look at it in making a productivity more efficient, leading to lower food costs for the consumer. We could argue that point a lot, as to whether that is right or not, but I would be very worried if there would be some group, a special interest group, in this case the farmworkers, who would rule that no university can do that research on mechanization because it has the potential to displace them.

I can appreciate the farmworker coming with that argument, but in terms of feeding the multitude, that might be a decision that would have a disadvantage to the majority. So that is the concern that I would have.

Mr. GORE. Briefly, Mr. Meyerhoff.

Mr. MEYERHOFF. I am intrigued that farmworkers have become a special-interest group.

The point is——

Mr. GORE. Well, under some circumstances they could be so characterized.

Mr. MEYERHOFF. Yes. The point is in the mechanization context. For example, if a Government official is deciding to spend public money to displace workers or to do scale-specific research that will benefit large landholders in California and place small farmers at a competitive disadvantage, those interests, have a right to know that that individual is not tied to companies that are in a position to directly economically benefit.

For example, in the University of California situation, the head of the Agricultural Experiment Station and the head of the Cooperative Extension Service, were on the corporate boards of TriValley Growers and Tejon Agricultural Corporation, two companies in a position to directly reap economic benefits from the development of these machines. There are many other examples.

I agree we should not debate the issue this morning, although I would love to.

Dr. HESS. Except the example you have given is guilt by association. In other words, the association is made, and the suggestion is made therefore, that the person would be making decisions which would benefit his or her corporation. And in the 7 years I have been at Davis, no one on the board of regents who was a member also of an agriculture firm has directed me to do some research that was in benefit of his interests.

Mr. MEYERHOFF. This matter will go to trial later this year, and we will get the answer.

Dr. HESS. Good.

Mr. GORE. The Subcommittee on Investigations and Oversight, incidentally, is planning a hearing this fall, perhaps a series, but at least one, on this generic question of how research priorities are set; again, not with a view toward affecting the result, but to throw light upon the process. And I take it that is the lowest common de-

nominator between the two of you. You don't disagree there ought to be greater light thrown on the process, and more openness in the process?

Dr. HESS. I have no problem at all with that.

Mr. MEYERHOFF. Dean Hess is quite different from a number of other university officials.

Mr. GORE. You mean there are some that disagree with that?

Mr. MEYERHOFF. I believe that is true.

Mr. GORE. Well, that is interesting.

Anyway, thank you both. We won't keep you any longer. We could continue not only this debate, but other interesting lines of inquiry that arise from your testimony.

I would like to thank you both for coming. I know it was some trouble to you. Thank you for the obvious preparation and thought that went into your statements. Thank you very much.

Mr. GORE. Our final panel today is made up of two witnesses, Charles Muscoplat, vice president for Medical Products, of Molecular Genetics in Minneapolis, Minn., and Mr. James William Chaney, vice president of Agrigenetics in Denver, Colo.

Let me say for the record again we invited Biogen to come and give its views, and it refused to do so voluntarily. We have chosen not to go through the procedures to compel testimony, but for that reason we doubly appreciate the willingness of you gentlemen to appear.

Without objection, the prepared statements of our witnesses will be included in full.

Dr. Muscoplat, if you want to begin, we would be delighted to hear from you.

STATEMENTS OF DR. CHARLES MUSCOPLAT, VICE PRESIDENT FOR MEDICAL PRODUCTS, MOLECULAR GENETICS, MINNEAPOLIS, MINN., AND JAMES WILLIAM CHANEY, VICE PRESIDENT, AGRIGENETICS CORP., DENVER, COLO., ACCOMPANIED BY R. N. DRYDEN, PRESIDENT, AGRIGENETICS CORP.

Dr. MUSCOPLAT. I received a letter in the mail suggesting some questions which I might address. Many of the points that I would have covered have already been raised by previous speakers.

I would have touched on the fact that university industry relations go back a long way, and there has been funding from industry to universities throughout this century. In recent times, with the advent of biotechnology, it has received a lot of attention in the press, and we read about the advances in biotechnology more in the Wall Street Journal than we do in the scientific literature.

The concerns that I would raise are exactly the same concerns that have been raised by the previous speakers.

The relationship between universities and industries does have some potential for conflict of interest in such situations where key people belong to both organizations. I have no magic insights how to solve those problems. But it is a point I would like to bring up.

From a personal viewpoint, as well as our company's viewpoint, we don't see it is wise to build the strength of a company on an outside individual, particularly someone who works at a university. It is not good use of resources. Such a person cannot devote full

energies to his work and the work at the university. So in a sense he cannot do justice to both jobs.

Arrangements with biotechnology companies differ from arrangements with other industries, such as the chemical, pharmaceutical or engineering industries. I think they differ in the sense that a chemical company may have hundreds of organic chemists working for them, and if they need an outside consulting organization they will go and retain organic chemists at some university to help them solve a particular problem. However, if a large industrial company wants to do research in biotechnology today, they don't have the in-house skills. They either have to go to small biotechnology companies or to universities to acquire many of the skills relevant to do that type of work.

I did want to make a comment that many ideas at universities do originate with people from industry. There is a lot of good science done in industries. There is always an exchange of ideas between university scientists and industry scientists, and ideas do go in both directions.

The second question that was on my list was; what are some of the difficult issues? Conflict of interest I think has been covered; allocation of resources, intellectual property, secrecy among faculty members. I think they all deserve comment.

I think we notice that when we talk to people today from our point of view as a company, some individuals are not willing to discuss scientific ideas freely. Individuals don't discuss data as freely as they may have in years past. A year ago I was a member of the university faculty. I have both perspectives well in hand.

We use consultants in many ways. We use them to find names of graduating possible doctoral fellows we might want to hire or previous students who have gone off and done other work and we track them down and get information from them, are they interested in coming to work for us, or can you tell us who is doing the good work today in some certain field of molecular biology or genetics, or can you get us some current literature, as well as inviting them in to give research seminars and symposia.

There are a number of ways in which industry makes use of university faculty for various purposes, as well as a novel use I heard of recently. One company that I know of, comprises an academic review board to come in and give comment on some of their ongoing research projects.

As far as the current techniques for commercialization of biotechnology, I think everyone should realize that biotechnology and genetic engineering is not a single discipline but rather a multitude of areas comprising virology, genetics, immunology, chemistry, engineering, clinical medicine, pharmacology, and the list goes on.

For example, to successfully commercialize a product, one has to be skilled in several different disciplines. It is hard for me to conceive how a university could take a product to complete development with limited skills in a certain department.

The gentleman from Monsanto pointed out very well that the wealth of talent at Washington University cannot be duplicated anywhere. But it is also hard for me to conceive how people within a university environment can take a project from inception to anywhere close to ccmmercialization, because of the multitude of dif-

ferent skills that would have to be assembled under one roof. So the real commercialization will have to be done in the industrial sector.

It is possible that there should be and could be good areas of cooperation between industry and universities. Given the fact that there needs to be such a multitude of disciplines to develop products in biotechnology, it may be difficult for one company to assemble all the different disciplines, and it may be wise to seek support in areas that are deficient within one company.

I think a lot of these things are going to change through time. We see today that there are approximately 150 small biotechnology companies. We see on the horizon there is going to be a shakeout and many of these will disappear or be acquired by large companies.

In addition, many large companies will recruit and establish their own in-house biotechnology programs which will make them less dependent on universities and smaller biotechnology companies for a continuation of their research. Many of the problems we face today with potential conflicts of interest, university people being drained away, may disappear in the future, as these large companies establish their own in-house programs and are less dependent on outside organizations, including universities.

As to what role the Government might play in insuring a proper return on the taxpayer's investment is made, my only comment would be, that gatherings like this to explore what are the facts, and how to generate suggestions as to what role Government might play are important.

I think there was a question, does our company have any plans to conduct cooperative research with a university? I think we probably do. It is not clear as to what that might actually be. I think it would probably be in line with my previous statement that a multitude of disciplines are required to develop products, and when we get to a point where we are deficient, we would probably go out and either do it with another company, or try to do it with a university, and structure some arrangement equitable to both parties.

The advantages and disadvantages of arrangements with universities: Obviously, to fill the needs of both parties, universities need to train students, supply funding and so on. Industry needs somehow to obtain the technology that it may not have in hand.

I think there should be a way, we should strive to find a way, that universities and industries can work together, especially in times of dwindling financial resources, for the universities. It would be nice to find a way to structure relationships whereby both parties can benefit from the interaction.

Another point that I did want to bring up is advantages of industry-university relationships. I know at the University of Minnesota they do use a large number of local industry people to teach courses at the university, at no charge from the industry. I think that is done all over the country. There is a lot of talent in industry. If it can be used by the university to beef up various teaching programs, reduce faculty burden of teaching time, and so on, it would be quite beneficial.

The last question on my list is, what role would you like the Federal Government to play in such an arrangement? I think it is too

early at this point in time for me to make any comment on that. I would like to see where these committees go with their responses.

Thank you.

Mr. GORE. Thank you very much.

Dr. Chaney?

Mr. CHANEY. Mr. Chairman, I would like to make a couple of corrections before I start my statement.

First of all, this will be a perspective of a seed company with a large commitment to genetic engineering, not a genetic firm.

I am a vice president of Agrigenetics Corp., a plant genetic research company which is engaged in the sale of agricultural crop seeds. I am also past president and director for life of the American Seed Trade Association, a member of the international and executive committees of that association, the vice president of the Federation of International Seedsmen, president of the vegetable seed section of that organization, and a member of its executive and steering committees. I have been in the seed business 33 years.

I am pleased to appear before you today, in response to your request to discuss university-industry interactions in the field of biotechnology, with particular reference to agriculture. My discussion will touch on some of the policies Agrigenetics Corp., has developed as a result of its research efforts, which include some sponsored research agreements with universities in addition to its in-house work.

Agrigenetics Corp. is a private, independent, investor-owned business corporation with principal offices in Denver, Colo. Our company currently has annual revenues of slightly more than $100 million deriving from the sale of more than 50 species of agricultural crop seeds in the United States and throughout the world. We have close to 900 fine employees who work in some 35 facilities, located in 13 different States. The oldest part of our company began business in 1845, and we can fairly say that we are familiar with the long history of agricultural research in the United States.

Agrigenetics believes that a unique opportunity currently exists in the use of new biotechnologies to meet the increasing global demand for food of better nutritional quality and to lower the cost of producing crops. While crop improvement has proceeded over the centuries through traditional methods of whole plant breeding, there is still much room for genetic improvement in performance potential, particularly through the use of new approaches deriving from cellular and molecular biology.

It is especially important to note that the biotechnologies promise to increase the amount of genetic variability in plant germ plasm. Agrigenetics takes pride in the fact that it is at the forefront in the use of biotechnologies towards the goal of crop improvement.

I will now attempt to answer some of the questions you have raised.

First, "How pervasive are industry-university arrangements in areas evolving in biotechnology? Do these arrangements differ from those in other scientific disciplines such as chemistry and engineering?"

Speaking only as to the agricultural aspect of biotechnology, it is my impression that these arrangements are not at all pervasive

and constitute only a minute portion of university-based agricultural research. I would guess that they represent approximately 1 percent of the total. This is also a small percentage of what is spent in industry-sponsored research at universities in the fields of chemistry or engineering.

I might add that such programs have a long-standing history and have proceeded for years without fanfare. I see no special reason for the unusual attention focused on biological technologies. In our opinion there is insufficient industry support of university work in the area of agricultural biotechnology, and the country would benefit if there were more of it.

Second, "How are universities dealing with difficult issues such as conflict of interest, allocation of resources, intellectual property rights, secrecy among faculty members et cetera?"

Mr. Chairman, it is important to realize that universities are like families. No two are alike. In the sound tradition of our social system, these issues are being decided by universities, administrators, and faculty members on a case-by-case basis, with the initiatives often coming from individual faculty members. While there are frequently a variety of opinions on how to meet some of these issues, there is every indication that they can be solved within the requirements of personal integrity on the part of scientists and within the requirements of public responsibility teaching and open research by the university.

While no two cases are alike, participants in emerging industry-university linkages are behaving in a sober and responsible manner. In our opinion, it is important to trust the intelligence and honesty of university scientists and administrators.

Third, "What are the current mechanisms for commercialization of biotechnology?"

In our opinion, biotechnologies are no different than any other scientific area. Commercialization of the biotechnologies depends upon our constitutionally-guaranteed rights to patents and free commerce. It is no different than commercializing technology in chemistry, physics or engineering. We see no reason for singling out biological technologies for special treatment.

Fourth, "What role should the government play in insuring that the proper return to the taxpayers' investment is made?

In our opinion, the Government should establish biotechnology as a national scientific priority. In the agricultural area, traditional U.S. Department of Agriculture-supported research in whole plant breeding may have reached a point of diminishing returns. The funding of innovative approaches to crop improvement promises to greatly increase our Nation's productivity, which is the most satisfying form of return on investment.

Fifth, "What are industries' needs in biotechnology, and how do they envision their roles in forming and implementing agreements with universities?"

Industry seeks two things—to be at the forefront of science and technology and to enjoy some form of proprietary right in exchange for supporting major research programs. Some people fear that exclusive rights may remove competition or retard development of technology or even prevent it altogether. This fear is exaggerated, in our opinion. Some form of exclusivity is essential if technology

99-177 O - 82 - 7

development is to take place, since no firm will expend large sums for development that will primarily benefit its competitors.

The secrecy issue, however, has been blown out of proportion. Patents actually eliminate the need for secrecy and, if delays in publication of scientific research are involved, one is talking about days or weeks, not months or years. Some universities are more concerned about secrecy restrictions advanced by Government than by business.

Industry's goal is the proprietorship of rights, not of information. With the analytic tools available today, scientific secrecy is, in any case, a transitory phenomena. Ironically, the absence of proprietary rights usually impairs rather than promotes the availability of useful technology.

It is right that, when appropriate, companies should acquire exclusive use of certain academic work. Without that exclusivity, companies would be most reluctant to commit their own funds for further development. In general, for every dollar spent on research, over ten are probably spent for development. If this issue of proprietary rights cannot be solved in a collaborative framework, industry will have little choice but to terminate sponsored research at universities and seek to do the same work 100 percent in-house, frequently by seeking to hire the same scientists.

If this were to become a trend, the scientific forefront would not exist at the university, and the teaching role of the university would be compromised. Few academic scientists, faced with deteriorating equipment, a diminishing supply of graduate students, and the need to spend more than one-third of their productive time scratching for funds, can long resist the appeal of gleaming instrumentation, high-speed computer backup, sizable budgets, and the promise of a more interdisciplinary approach to research.

Sixth. "Does your company have any plans to perform cooperative research with a university?"

Agrigenetics presently sponsors cooperative research at a number of institutions. In many cases our company was approached by university scientists seeking direct support for their work. At the present moment, a number of agreements are in negotiation.

Our attitude toward sponsored research is somewhat experimental and, if this experiment in cooperative research does not work out, we would do more of this work in-house. We have the facilities and equipment and funds to do so. It is our view that these agreements must not promote secrecy, impair the educational experience of students, diminish the role of the university, interfere with the choice of scientific issues addressed by investigators or divert the energy of faculty or the resources of the university from their primary educational and research missions.

Seventh. "Describe, as you perceive them, the advantages and disadvantages of arrangements with universities."

In general, the advantage is principally being involved in the forefront of research. In general, the disadvantages are absence of control and the understandable problems of trying to mesh two cultures into a fruitful collaboration.

Eighth. "What role would you like the Federal Government to play in such arrangements?"

First of all, the Federal Government should regard corporate dollars as complementary, not supplementary, dollars. In this regard, they should spend more dollars on basic plant science as in the USDA competitive grants program. This has the advantage of avoiding start-stop approaches to research and takes the long-term view so as not to get hung up in the morass of annual budgeting. In designing these programs, the Government should strive to increase the use of peer review for academic research in plant science and to minimize paperwork for scientists.

A good bench mark for the role of the Federal Government is to compare what we are doing with what the Japanese, the Germans, the British, and the French are doing in this area.

In conclusion, it is our opinion that the university community has a social obligation to try to promote technology transfer and that it has to do so in ways that do not jeopardize the search for knowledge for its own sake. In the United States, the options continue to lie within the framework of a system of private enterprise, and, because of the changing pattern of Government support of scientific research, universities are obligated to try to find additional sources of funds both to preserve their autonomy and to prevent a waste of trained scientific talent.

If universities are to protect their financial base in order to advance their social and academic goals, they will have to find imaginative adaptations and take a tough-minded attitude toward the breakdown of ivory towers. Whatever risks exist must be balanced against the financial insecurity of academic departments and a monolithic dependence on an often unsympathetic and highly bureaucratic government.

The handful of agreements that do exist, for example, between Du Pont and Harvard University, Exxon and the Massachusetts Institute of Technology, Mallinkrodt and Washington University, and Monsanto and Rockefeller University, suggest that it is unlikely that universities will be able to sweeten the terms in their search for industrial support. The areas of research are appropriately basic, the freedom of publication is actually unencumbered and the institution gains some permanent resources. These agreements allow the universities to do what they do best, basic research, and it allows industry to do what it does best, develop useful products.

In the challenge to maintain technological and economic leadership, the United States must strengthen the linkage between research and innovation and between the principal institutions involved, universities and industry. The generation of knowledge and its translation into products and services depends on a linking interaction between those who perform basic research and those for whom the results of basic research are the raw materials for product development and commercialization. Strong university-industry relationships can enhance the basic research innovation linkage.

In the final analysis, the key to effective interaction between universities and industry is a scientist-to-scientist contact on the research matters that commonly exist and a reliance on the integrity of individuals.

Thank you, Mr. Chairman.

Mr. GORE. Thank you very much.

Mr. Dryden, you don't have a statement, is that correct?

Mr. DRYDEN. That is correct.

Mr. GORE. We have a vote on the floor. I think this would be a good time to break. It will only last 6 or 7 minutes. Then we will finish up with the questions for this panel when we come back in.

[Recess.]

Mr. GORE. The subcommittees will come back to order.

Mr. Walgren left the following question that I would like to ask in his behalf.

Several witnesses have commented that large companies do not now have strong in-house scientific staffs in molecular genetics, and that this has led companies to establish ties with universities which do have strong scientific groups.

This is evidence of a shortage of manpower. This is not suprising in the short run, because molecular biology became commercially interesting rather quickly.

What is being done by companies to help universities solve this manpower problem in the longer run, and is there a risk that industrial interests could make the manpower situation worse by diverting professors from training students?

Dr. MUSCOPLAT. I will try to answer that one.

I think it is a concern. We have talked about it at our company on a number of occasions. We think that there is a shortage today, and there will probably be a greater shortage in the future, partly because some of the mentors who would be training students have since left universities and they are no longer training these bright young students to take their place at universities or in industry.

It would be desirable, I think, to find a way to funnel money back into the universities in training programs or for the government to increase funding in training programs to make sure these students do get trained in the future, so we meet manpower needs of the future.

This is a young industry, and it is dynamic and changing. The kind of molecular biologies we have today, or the kind of biology we do today, may not be the same in 5 years. It would be analagous to the microcomputer and semiconducter. The science is changing yearly. It is important that we keep the training programs dynamic as well.

Maybe it is an obligation of the industrial concerns to put back some money into the universities to help in the training of future individuals.

Mr. GORE. You mentioned that you yourself were a university professor?

Dr. MUSCOPLAT. I was. I was a professor of veterinary medicine at the University of Minnesota up until last year.

Mr. GORE. If I may ask, how did you arrive at your decision to leave—well, to the extent you care to tell us.

Dr. MUSCOPLAT. I will try to describe it.

I think my career goals as a professor of veterinary medicine were in the delivery of animal health care and development of vaccination and preventive programs for animal health. Working with a company such as Molecular Genetics, who's main goal is to develop animal health products, and who also has sufficient resources, it was a great opportunity to continue my career goals and see ideas implemented.

Staying at the university with limited resources, it was very unlikely we would have realized any of our ideas.

Mr. GORE. Now, presumably the other goals you were pursuing at the university, teaching of students, training of others for the future, are now not being pursued by you in your new situation.

Dr. MUSCOPLAT. That is correct.

Mr. GORE. The same question, Mr. Chaney.

Mr. CHANEY. Yes. We do have in-house capabilities, but may I defer this question to Mr. Dryden?

Mr. GORE. Sure.

Mr. DRYDEN. If you break your question into two pieces, first is there sufficient availability of manpower? From our perspective, we have found no shortage of highly qualified scientists. I think that is true for big corporations as well as those our size. There is naturally a lot of stiff competition among the various companies for the most qualified scientists.

As for the second part of your question—whether there is a diversion of the teaching staff within universities—the answer is yes, but this is just as though some people prefer to be a politician as opposed to a doctor or lawyer or to pursue a different goal within the same field.

There are definitely scientists who, for pecuniary reasons or the exact same reasons that Chuck has alluded to, have decided to go into industry. This is the more important problem, as to whether the qualified teaching staff is still going to reside in the universities to educate the future generations of scientists.

Mr. GORE. Well, we explored in hearings last week some of these manpower problems. When a company like yours, Mr. Chaney, offers a postdoctoral student a good deal, it is understandable that they will take you up on it. The consequences for the university they leave in fields that have a manpower shortage are, I think, cause for concern.

Mr. CHANEY. Well, Mr. Chairman, I think that this is a very real concern, and it is one that concerns Agrigenetics.

That is the reason we have chosen the route of going to universities for some of our research rather than hiring scientists to come to our facilities. We have a marvelous research facility in Madison, Wis., which, with 30 or so Ph. D's plus a complement of plant breeders in each of divisions, takes the basic research into commercial reality.

We think it is of benefit to the country and to the universities to take that research to them, fund it there, and let them stay in academia, and be of service thereto.

Mr. GORE. Well, in that regard, we heard from Dr. Winston Brill last week on the subject of recombinant DNA and its applications to agriculture.

As I am sure you know, Dr. Brill is research director of Cetus Corp. in Madison, a biotechnology firm, and also remains a professor of bacteriology at the University of Wisconsin.

We understand that Dr. Tim Hall, who is associated with your laboratory, was recently forced to take a leave of absence from the University of Wisconsin, whereas Dr. Brill is still there wearing two hats, so to speak.

Do you feel that your company was discriminated against in this regard?

Mr. DRYDEN. No. As Bill said in the statement—each university must be viewed as an individual case, and they are like individual families. And even when you get within that family——

Mr. GORE. This is the same university, isn't it?

Mr. DRYDEN. Even when you get within the individual family, there are individuals with different personalities. You find at the University of Wisconsin, as at many, that the rules are set at the departmental level. We don't feel as though we were discriminated against. It is just the way that the chips fell. Tim happened to be in that particular department, and Winston was in another, and John Kemp, another of our research directors from the University of Wisconsin, was in yet a third.

Mr. GORE. Is Dr. Kemp still with the univesrity?

Mr. DRYDEN. They are both on leave of absence.

Mr. GORE. So both Dr. Hall and Dr. Kemp were required to take a leave of absence, and Dr. Brill was not. What is the distinguishing characteristic between Dr. Brill and the other two cases?

Mr. DRYDEN. Simply which department they happened to be in.

Mr. GORE. Do you think that they made the wrong decision with respect to Dr. Hall and Dr. Kemp?

Mr. DRYDEN. No, not in particular. I am not going to second-guess the university in making decisions it thinks are important to its departments.

I will say, by the way, Dr. Bock, who is going to be speaking here tomorrow, is the most appropriate individual to give you the university's point of view.

Mr. GORE. Did some of the graduate students of Dr. Hall and Dr. Kemp also leave the university to come to your company when they left?

Mr. DRYDEN. Yes, sir.

Mr. GORE. Well, I guess we will ask the university how that affected them as well.

Mr. DRYDEN. I have to say, by the way, I think's both in the case of Cetus Corp. and Agrigenetics the relationship between our companies and the university is one that has matured and is fitting a very satisfactory a natural mold.

Mr. GORE. Mr. Chaney, you state that the United States must strengthen the linkage between universities and industry to maintain technological and economic leadership. What could or should the Federal Government do to strengthen this linkage?

Mr. CHANEY. Well, I think one of the first things it can do is give a higher priority to universities for basic research. This would of course strengthen the relationship between industry——

Mr. GORE. So the best thing we could do is to make a bigger commitment to basic research, and we would avoid some of these problems and serve the needs of our industrial base at the same time?

Mr. CHANEY. As you know better than I, many foreign countries have a very, very strong commitment to agricultural research, much stronger than the United States. They think first about bread.

Mr. GORE. Dr. Muscoplat, your company recently had a public offering of common stock, is that correct?

Dr. MUSCOPLAT. That is correct.

Mr. GORE. A couple of years ago, when Genentech went public, you remember there was a phenomenal first day ride. You did not have this experience, did you?

Dr. MUSCOPLAT. No. The market hasn't been shining lately.

Mr. DRYDEN. But it should be noted that their stock has held.

Dr. MUSCOPLAT. Yes.

Mr. GORE. The point of my question is, does that reflect a mature attitude in the market or what?

Dr. MUSCOPLAT. It is probably a more realistic attitude in the market. There are a lot of companies out there in the public marketplace, and the investor has a choice now. I think when Genentech came to the marketplace, they were the only play, and the investors saw that as the only play for the moment, and the stock rose accordingly.

Mr. GORE. Well, do you think that the gold rush, so to speak, is over in the world of entrepreneurial genetic firms?

Dr. MUSCOPLAT. I think for somebody who has a very good idea, a really good and novel idea, there will be a way to get it funded today, in biotechnology, for some time to come. I think that another me-too approach, given the fact there are 140 or so biotechnology companies, the prospects are not as good for those types of companies. I think the market valuations of companies reflect what people perceive as the productive and profit potential of these companies.

I guess I am a believer that the biotechnology business is a good business and is generating products, and will be good business to be in and a good investment today.

Mr. GORE. Well, thank you.

One of the elements in this debate has been the diversity of orientation of the entrepreneurial firms like your own toward universities. While some, like yours, Mr. Chaney, are across the street from a campus, the private and public impression that the subcommittee have been given by other firms is that dealing with commercial neophytes from the academic community is too much trouble and many tend to shy away from it.

Do you have any comment on that, briefly?

Mr. CHANEY. Well, I would briefly say that the seed industry does not have a consensus of opinion on this question at this time. It depends on where they are coming from, maybe not where they live, but what kind of business they are in, if they have their own research program, if they are capable of funding it themselves, where they depend on public research for their varieties. Here again it is a private thing, with a private company. But we cannot come to a consensus in the American seed trade, for example, about this.

Mr. GORE. OK.

Well, I guess I will follow up. I had some other questions, but I think your suggestion is appropriate, that some of these questions relating to the university's point of view, since we are going to have the University of Wisconsin tomorrow, might be more aptly addressed to them.

But I am curious that we have these three scientists, two of them working for you, and they are required to leave the university, and

another one present with another company, is allowed to stay on and the distinction seems to be that different departments have different policies.

The university as a whole does not have a policy in this regard?

Mr. DRYDEN. I think the university's policy is to let the departments set policy. I believe you will find that they have very good reasons for this policy.

Mr. GORE. Well, all right. Let me thank you all for your contribution here today. We appreciate it very much. This is a difficult subject, as you well know. We are indebted to you for helping us understand it better.

Tomorrow we will convene at 1 p.m. for the continuation of these hearings.

[Whereupon, at 2:02 pm., the subcommittees adjourned, to reconvene at 1 p.m., Thursday, June 17, 1982.]

UNIVERSITY/INDUSTRY COOPERATION IN BIOTECHNOLOGY

THURSDAY, JUNE 17, 1982

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY,
Washington, D.C.

The subcommittees met, pursuant to call, at 1 p.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the Subcommittee on Investigations and Oversight) presiding.

Present: Representatives Gore, Brown, Dymally, Walgren, and Walker.

Mr. GORE. The subcommittees will come to order.

Yesterday we heard, through two case studies, testimony on the ways in which universities and industries are interacting in the commercialization of biotechnology. Conflict of interest problems for participating faculty members posed by the University of California at Davis and Allied Chemical agreement are issues that most universities will have to confront in their agreements with industry in one form or another.

One suggested solution was that the Federal Government in granting money to universities require that faculty members disclose their sources, both public and private, to assure that no conflict of interest exists.

The Monsanto-Washington University agreement provided interest and excitement as it actively involved the university in the planning and selection of projects and, moreover, provides for an outside scientific review of the joint agreement after 3 years to assess its success.

Today we will hear the perspectives of two Government agencies which fund the majority of all basic science research projects in this country, and from university officials who have to grapple with the ethical and institutional concerns that we have been exploring.

We look forward to their testimony this afternoon and I would like to ask unanimous consent to insert into the record at this point an opening statement of my cochairman for these hearings, Mr. Walgren. I would be delighted at this time to recognize my colleagues, if they have any opening remarks.

Mr. GORE. If not, we will go straight to the first panel for the university perspective, Dr. Robert Rosenzweig, vice president for public affairs at Stanford University; Dr. Robert M. Bock, dean of the graduate school at the University of Wisconsin and Dr. Roderick B. Park, vice chancellor of the University of California at Berkeley.

Dr. Rosenzweig is representing the views of the AAU as well as his own, Dr. Bock is representing the viewpoint of scientific associations and Dr. Park is representing Berkeley.

Without objection, the prepared text of all three witnesses will be inserted into the record in full. Dr. Rosenzweig, if you would begin with your presentation, we would appreciate it. Let me welcome you and also thank you for the numerous discussions that you and I have had about this issue on an informal basis for some time now. It is a delight to see you here in this more formal context.

Please proceed.

[The opening statement of Mr. Walgren follows:]

OPENING STATEMENT
HONORABLE DOUG WALGREN
HEARING ON
UNIVERSITY/INDUSTRY COOPERATION
IN BIOTECHNOLOGY

JUNE 17, 1982

I WOULD LIKE TO WELCOME YOU ALL TO THE SECOND DAY OF THE HEARINGS ON THIS IMPORTANT AND TIMELY SUBJECT.

YESTERDAY WE HEARD SOME VERY INTERESTING TESTIMONY CONCERNING TWO SPECIFIC INDUSTRY-UNIVERSITY ARRANGEMENTS. ONE (WHICH INVOLVED THE UNIVERSITY OF CALIFORNIA AT DAVIS, ALLIED CHEMICAL, A SMALL ENTREPRENEURIAL COMPANY NAMED CALGENE, AND A UNIVERSITY OF CALIFORNIA AT DAVIS RESEARCHER, DR. RAY VALENTINE) HAS BEEN RESOLVED BUT NOT WITHOUT SOME UPHEAVALS AMONG STUDENTS AND FACULTY AT UC-DAVIS AND AT SOME COST TO THE UNIVERSITY AND THE INDUSTRIES AND, NOT LEAST OF ALL, DR. VALENTINE.

PERHAPS IT WAS THIS INCIDENT THAT INFLUENCED TO SOME EXTENT THE CREATION OF THE SECOND AGREEMENT, THAT BETWEEN WASHINGTON UNIVERSITY IN ST. LOUIS AND MONSANTO COMPANY. THE STRUCTURE OF THIS ARRANGEMENT, AS WE HEARD FROM TWO ELOQUENT WITNESSES, ATTEMPTS TO SAFEGUARD THE BASIC MISSION OF THE UNIVERSITIES--EDUCATION AND RESEARCH IN AN ATMOSPHERE OF THE FREE AND OPEN EXCHANGE OF IDEAS--WHILE AT THE SAME TIME STRIVING TO ENHANCE INNOVATION AND THE

TRANSFER OF BASIC TECHNOLOGY INTO SORELY NEEDED HEALTH CARE PRODUCTS. WE HOPE THAT THEIR APPROACH, HERETOFORE UNTRIED, OF SUBJECTING THIS CORPORATE SPONSORSHIP TO PEER REVIEW WILL SUCCEED; AND PERHAPS IF IT IS SUCCESSFUL MAY EVEN SERVE AS A MODEL FOR OTHER INDUSTRIES AND ACADEMIC INSTITUTIONS STRUGGLING WITH THESE SAME QUANDARIES.

WE ALSO HEARD FROM TWO SMALL BIOTECHNOLOGY COMPANIES, AGRIGENETICS AND MOLECULAR GENETICS, BOTH OF WHOM HAVE ARRANGEMENTS WITH UNIVERSITIES OR INDIVIDUAL MEMBERS OF THE FACULTY. IT WILL BE MOST INTERESTING TO WATCH THE MATURATION OF THE BIOTECHNOLOGY INDUSTRY (THE "SHAKEOUT", AS IT'S TERMED) OVER THE NEXT FEW YEARS AND HOW IT AFFECTS THE CONDUCT OF INDUSTRY-SPONSORED UNIVERSITY RESEARCH IN THE BIOTECHNOLOGIES.

TODAY WE WILL HEAR FROM THE MAJOR FEDERAL GRANTING AGENCIES, FROM A MAJOR RESEARCH UNIVERSITY AND FROM SCIENTIFIC AND ACADEMIC SOCIETIES. OUR FIRST PANEL WILL INCLUDE DR. ROBERT ROSENZWEIG, VICE PRESIDENT FOR PUBLIC AFFAIRS AT STANFORD UNIVERSITY, TESTIFYING ON BEHALF OF THE ASSOCIATION OF AMERICAN UNIVERSITIES. ALSO ON THE PANEL ARE DR. RODERICK PARK, VICE CHANCELLOR OF THE UNIVERSITY OF CALIFORNIA AT BERKELEY, AND DR. ROBERT BOCK, DEAN OF THE GRADUATE SCHOOL AT THE UNIVERSITY OF WISCONSIN, TESTIFYING ON BEHALF OF THE AMERICAN SOCIETY OF MICROBIOLOGY AND THE FEDERATED AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY.

STATEMENTS OF DR. ROBERT ROSENZWEIG, VICE PRESIDENT FOR PUBLIC AFFAIRS, STANFORD UNIVERSITY; DR. ROBERT M. BOCK, DEAN OF GRADUATE SCHOOL, UNIVERSITY OF WISCONSIN; AND DR. RODERIC B. PARK, VICE CHANCELLOR, UNIVERSITY OF CALIFORNIA AT BERKELEY

Dr. ROSENZWEIG. Thank you, Mr. Chairman. It is good of you to ask me to come today. I have enjoyed those conversations, too, and learned from them and enjoyed the arguments we have had from time to time on some of these matters. I think since I have a quite brief statement, it would be a good deal more expeditious simply to read it than to try to paraphrase it, because it would almost surely turn out to be longer if I try to paraphrase it.

Mr. GORE. All right.

Dr. ROSENZWEIG. A good deal has happened since November 18 of last year when Mr. Gore and Mr. Fuqua wrote to Dr. Thomas Bartlett, president of the Association of American Universities to ask that the association "take the lead to draft ethical guidelines that will enable us to grapple with these and future issues forthcoming from such close university-industry ties."

One of the things that happened, and I assume that it is the one that brings me here today, is that Dr. Bartlett asked me to chair a committee that would recommend to the members of the association the proper stance for them to take, as an organization, toward these issues. My report on the work of the committee can be short. We have met twice, we have assigned responsibilities for drafting portions of our report, the report will be put together over the summer, and we hope to have it to the AAU members in time for their fall meeting in October.

I wish that I could be more substantive in this report, but if I tried to be I would be inventing it, not reporting it. Perhaps, though, I can be helpful to you by describing briefly some of the other developments of the last 9 months, because they provide a part of the context within which the AAU will do whatever it finally decides to do.

By far the most important contextual development of the period is the extraordinary number of words devoted to the various issues involved in industry-university agreements. These have been written and spoken in newpapers, magazines, professional journals and meetings, conferences, and perhaps most important, on individual campuses.

I have to admit that it is not news that academics talk a lot, and that we frequently deal with our problems by throwing words at them. That very fact makes the attention given to these issues a significant happening. To suggest just how significant it is, I would call your attention to the contrast between the present circumstances and those that accompanied the reshaping of university-based research through the growth of large-scale Government support. Universities were literally transformed in that period, and so was the way in which fundamental research is generated, supported and even conducted. Yet one is hard put to it to find very much serious thought about the consequences of it all.

I have had occasion recently to go through some of that literature and I can attest to that from firsthand experience.

More typically, the attitude in the academic world—at least in the scientific part of it—was that it was all simply a natural and long overdue recognition of the virtue of the activities being supported and of those who did them. Indeed, very little serious thought was given to the nature of the relationship that was emerging between universities and the Government until that relationship began to develop strains, not the least of which was tightening of the purse-strings.

That record stands in sharp contrast to the serious, critical, and voluminous attention that has been lavished on the growth of the much smaller, and probably less important, connections that are emerging between universities and industry. Let me be clear that I view the earlier record as harmful to the health of universities, research and public policy and that I view the contemporary scene as healthy and heartening for all of those. We may not find the right answers, but it is highly likely that all of the right questions will be asked and that a wide range of answers will be examined and debated.

Among the questions that have been on the agenda in recent months are the following: Are institutional policies with respect to faculty consulting adequate to the present demands on them? Do they adequately balance the desirability of having faculty productively connected to the world of affairs and the need of the institution to protect against an unacceptable dilution of the faculty's attention to their primary responsibilities? Do policies on the disclosure of faculty consulting properly balance the right of privacy of association and the protection of the institution and the public from conflicts of interest? Is it possible to balance the need of business occasionally to protect information of proprietary value with the need of science for open communication? Are new policies needed in order to protect graduate students from becoming unwitting agents of their professors' commercial associations?

My sense is that it might be premature to assert general answers to these and similar questions, but I could be wrong in that. I know that these matters are being actively debated on many campuses, and that different answers will emerge from those debates. Those who are certain that only one answer is possible would do well to examine those that will emerge from the deliberations of serious and honorable people in different places.

You will recall that the report of the group that met at Pajaro Dunes in March was informed by that spirit. To reach closure too soon on complicated issues that bear differently on different institutions might well inhibit the many discussions and debates that need to take place around the country if policies are to reflect reality rather than emerge from ideology.

We are not, however, rudderless on a dark and stormy sea. There is, I believe, substantial convergence on a set of principles that should guide the formulation of policy. I would list the following: Openness is to be preferred to secrecy; the educational experience of students and postdoctoral fellows has priority over the need to fulfill commercial obligations; university policies should protect the role of the institution and its faculty as credible and impartial resources in debates on scientific and technological policy; the choice of scientific questions to investigate must reside with the faculty

who will do the research; and the primary obligations of faculty members are to their teaching and research.

A serious effort to be faithful to such principles will, I believe, yield sound policies, even though the particulars of policy will vary from place to place and even though deviations from principle are always possible in an altogether too imperfect world.

I will close with some brief comments in response to the specific questions addressed to me in your letter of June 10, 1982. You asked about the general feeling among university people with regard to forming more arrangements with industry, and you asked specifically about the attitudes in the institution that I represent, Stanford. In both cases I think that reality has begun to assert itself. We have begun to see our relations with industry less as a bonanza that will save us from losses in Federal funding of basic research, and more as important supplements in particular fields in which current work happens to be of mutual interest. Very few people think that the very large and highly publicized contracts are likely to be duplicated very widely or to become anything like the norm.

As expectations of gain become more modest, thinking about the risks in these arrangements has become more focused and useful. The threat to institutional autonomy and to the integrity of scientific inquiry that grows out of the uneasy mixture of academic and commercial values is real enough. This committee and others have called attention to the ways in which that threat might take shape. But it is by no means a new threat. Indeed, it is really a new manifestation of a central theme in the history of American universities, namely, the continuing tension between the life of the mind and the world of affairs. At least since the passage of the Land Grant Act, that tension has been a source of great creative energy and of recurrent danger within our institutions, both public and private.

Both the creativity and the danger exist in the present situation, and I believe that we can, as we have for so long, continue our successful high wire act between the two. We can, that is, if we allow ourselves the time and the space for good sense to prevail. If, however, we allow ideology—by which I mean fixed notions about the intrinsic nature of business or universities which lead inevitably to fixed prescriptions to govern their conduct—to rule, then I would guess that we stand to make some serious mistakes.

Finally, it is in exactly that context that I would view the role of government. Watchfulness is surely in order, accompanied by probing questions and an insistence on thoughtful answers. But when it enters the regulatory mode, Government finds it hard not to deal in answers of general applicability. If I am right, we do not need or want such answers. In my view, we will do much better for ourselves if we allow ourselves to draw on the best in our history and traditions, even at the risk, indeed in the knowledge that we will make some mistakes along the way.

Thank you, Mr. Chairman.

Mr. GORE. Thank you for a thoughtful statement. We will withhold questions until the panel has completed its statements.

I am itching to ask some. One of your principles seems to conflict with the landmark new agreement that was announced recently between Monsanto and Washington University.

Dr. ROSENZWEIG. I thought you might notice.

Mr. GORE. I did notice it, but I will hold back questions.

Dr. Bock, dean of the graduate school of the University of Wisconsin, we heard some testimony about your institution yesterday and I know you are representing a scientific association, but I trust that you are representing your own views as well and we are delighted to have you.

Please proceed.

Dr. BOCK. Very much so. In fact, a large scientific association such as the Federated Societies for Experimental Biology doesn't have a single opinion and so I really am representing myself, but my experiences with that society as well.

I will try to summarize and highlight by example some of the points in the prepared presentation I have given you. I do want to mention that I am a molecular biologist and I do still conduct research and my students routinely use genetic engineering to solve problems of basic biology as the tools fit the need.

Genetic engineering has become a very welcome tool to answer important basic questions. I am aware that it is opening very important potential applications for the benefit of all of us.

I would like to observe that the United States has pattern of support of research that evolved largely since World War II. The experiences during World War II on the responsiveness of universities in placing their wide range of skilled scientists on projects serving the Nation's need was a very welcome one. The Office of Naval Research, a shining example of research support during that period, and Government and university leaders were impressed that university-Government partnerships offered an opportunity that should be developed.

We now see that this Nation has developed a pattern of placing much of its basic research in a university setting with the National Science Foundation and the National Institutes of Health as the two agencies most heavily focused on basic research. The mission agencies such as Defense, Energy, Interior, and Commerce invest in basic research when they find that there is an area of the deficiency in knowledge that is necessary for their mission and they have made very important contributions to our broad understanding of scientific phenomena.

I believe that fundamental research serves our Nation best when it is available to all of us in the open literature. We are not smart enough to know how a basic discovery in one field will impact other fields, and any attempt to compartmentalize knowledge and discoveries causes more disservice than it does service. Thus, openness should be a general principle toward which we all subscribe. The results of basic research should be published promptly and clearly in useful terms and transmitted to potential users in ways that are indeed intelligible and useful. It is quite appropriate that our agencies expend a small percentage of their budgets in seeing to it that technology is transferred to the Nation's best interests.

NIH does this almost automatically because so much of its research is conducted in the research hospitals and in the training

settings for persons who will use this new knowledge. So the medical schools, the research hospitals are a locus of, perhaps half of all of NIH's research and these are the training grounds for the consumers of that new knowledge. Technology transfer is an intrinsic part of the NIH research funding strategy.

The National Science Foundation has found a number of ways of encouraging technolgy transfer including joint research projects between industry and universities, workshops, and conferences. NSF has recently published for comment a statement of principles for the involvement of industry in National Science Foundation-supported facilities.

I believe this NSF statement was a constructive and thoughtful action.

I believe that our patent process must work promptly and well in order to form an important keystone in the transfer of technology from basic research laboratories into the marketplace where it is available to the general public. Incentives for inventors to take the extra effort to see that their results are communicated to the users in the marketplace are also necessary.

Without adequate patent protection, I think that we stand to lose a great deal of the benefits of scientific research. We are all aware that regulatory delay in certain sectors of our new science and technology are very great, particularly when they involve the treatment of man with new procedures. The delays have been as long as a decade or more between the time of a clear discovery and the first time that it is deliverable to the general public.

This has been a disincentive to industry to develop activities that they know are controversal or orphan or very novel and exploratory. I believe that the Congress has addressed this issue and are attempting to correct some of the problems and some of the disincentives of the current patent protection system when areas are harmed by regulatory delay.

Also the system of patents and copyrights is an evolving system that depends on precedent and example. Some of our fields, particularly computer software and genetic engineering, are moving so fast that there isn't a precedent and we can't wait for precedents to be established while we are attacking a half a dozen particular issues at one time. The rapid pace of change is stressing our legal system on the interpretation of patent policy.

This will correct itself automatically as we gain more experience. There are fascinating new questions about the changing technology. There are times when all of us would agree that a mathematical equation, a principle of mathematics that solve a problem efficiently and concisely was not a patentable activity. What if that equation is translated into a specific piece of software or hardware in computer technology that has a great advantage over previous computers? The intellectual contribution was made by hard-working scientists. Should they have a reward for this effort or not? Under the current patent system it is not clear that they have any possibility of being rewarded.

I would like to comment that industry can and will support research, including basic research in appropriate situations. We are all aware that Bell Laboratories, Du Pont, IBM, Boeing, General Electric, General Motors, Honeywell, Minnesota Mining & Manu-

99-177 O - 82 - 8

facturing and perhaps another dozen companies are shining examples of excellence in research.

However, look at the Fortune 500 list of corporations. You won't find that 10 percent of the Fortune 500 are significant investors in research, even the applied research necessarily for their own areas. It does not appear practical to ask that each industry take care of its own research needs.

The fragmentation of knowledge and the general usefulness of new knowledge for industry and the public broadly demonstrates that there is a major and necessary Federal role. There are mechanisms by which industries join together in associations looking at common problems and in those associations they often attack basic research to a much greater degree than they could as individuals. The Petroleum Research Fund, the Association of Pulp & Paper Industries, and the Electric Power Research Institution are examples. However, past interpretation of the antitrust laws or their enforcement has inhibited industry from working together on common interest problems.

It is possible to live within the spirit of the antitrust laws and work together within industries providing that the results are not made exclusively available on a long-term basis to the participants in that cooperation. There must be mechanisms which are reasonable that generate this information for the broader consuming public.

That is quite proper and so we see that there are opportunities for industrial consortiums to come together to support research that serves their needs. It is clearly evident that our steel industry, our insurance industries, our transport industries, and others need to spend a concerted effort together. They should be encouraged to work together to solve the serious problems which have caused disadvantages to the public because these industries are inefficient deliverers of service or unable to compete with foreign industries.

I would encourage universities to work with industry under traditional grant and contract mechanisms whenever possible. Use the old and established contract mechanisms that are used with foundations and Federal funding agencies. Look for a partition of labor so that the university does not engage in industrial activity (that is, not in delivery of services, not in short-term product development tailored to the marketplace) but only in those activities that are reasonable training opportunities for their students and that contribute to the broad general knowledge.

So I think that a division of labor will solve many of the problems concerning proprietary information and openness of results.

I have brought along and will be delighted to make available to the committee for their use some additional documents.

For example, the conflict of interest statement that was last modified substantially in 1975 at the University of Wisconsin. It is a statement of the rules regarding outside activities and faculty ethics and it describes policies on the use of facilities which serve well for the use of federally supported facilities as well as the university's own facilities.

I have also brought along a copy of the National Science Foundation Industry facilities policy, but it is published in the Federal Register and I could just call your attention to that publication.

I have brought along descriptions of the Wisconsin Alumni Research Association, a licensing and patenting arm of the university which has served us well for over 50 years and has fed back to research at the university over $100 million of return from the inventions of our faculty. WARF's licensing policy is carefuly monitored to serve the public good.

I have also brought along a document which we distribute to our faculty about how the Wisconsin Alumni Research Foundation will help that faculty in the distribution of genetic materials. This is an effort to comply with the intent of NIH and NSF to make materials available, have some benefit return to the investigator, and to impose no cost to NIF or NSF for such a distribution.

We did this in anticipation that there will be clearer policies, but we think we have served the intents.

So I would be delighted to make such documents available for the use of the committee and I would be glad to answer any questions.

[The prepared statement of Dr. Bock follows:]

Statement for Joint Subcommittee
Hearing on University/Industry Relations

by

Professor Robert M. Bock
Department of Biochemistry
and Laboratory of Molecular Biology
University of Wisconsin-Madison

Congressman Gore, Congressman and members of the Subcommittee: thank you for the opportunity to comment regarding my experience on this topic. I conduct research on the basic structure/function relations in transfer RNA, the molecule which translates nucleic acid messages into protein products. I use genetic engineering methods when appropriate to answer basic questions and I am well acquainted with the potential of these new tools for improving existing industrial practice and for opening new areas for the benefit of mankind.

I chair the Federated Societies for Experimental Biology Public Affairs Committee, and have served on government relations committees for the Council of Graduate Schools, the Land Grant Association and the Association of Graduate Schools. I wish to thank the American Society for Microbiology for urging me to participate in this hearing.

As Dean of the Graduate School at Wisconsin, I chair the faculty committee which reinvests into further research the income from patents secured by WARF (Wisconsin Alumni Research Foundation) for our scientists. Over $100,000,000 of WARF income has been reinvested in research in the past 50 years.

Following World War II, the United States evolved a distinctive pattern for using higher education institutions as the locus of much of the nation's basic research and the government established NSF and NIH as two cornerstones of that process. This mode is efficient, highly adaptable to new concepts, accomplishes training while conducting research and is now emulated by Mexico, South Korea and other emerging high technology nations.

The NSF and NIH are two agencies most heavily focused on basic research. Mission agencies such as Defense, Energy, Interior and Commerce invest primarily

in applied research and development, but when a clear need for basic understanding is related to their mission, they do invest in topic-focused basic research.

The results of fundamental research serve our nation best when openly available to all potential users. Ideally, results are published promptly, described in clear and useful terms and transmitted to potential users in such a manner as to assist them in incorporating new concepts into their activities. Agencies' investment of a small percentage of their research budgets to encourage technology transfer appears to be in the nation's best interest. NIH assists this transfer by supporting research in the hospitals and clinics which are major users of research results for patient care. NSF encourages technology transfer in several ways ranging from conferences and workshops to shared facilities, to joint research projects between industry and universities. NSF has recently published a statement of principles for the involvement of industry in NSF-supported scientific facilities. I applaud this thoughtful and constructive NSF action.

Recognition and rewards to inventors and developers of new technology are important factors in encouraging innovation and movement of new concepts into the marketplace. At the University of Wisconsin, the specific inventors, their academic departments and all researchers at the University benefit from our patent and license income. Adequate patent protection enables industry to engage in costly development and marketing efforts. Without such protection, secrecy becomes necessary and the scientific findings are not widely shared. Secrecy is not appropriate for an educational institution engaged in basic research and the dissemination of knowledge.

Regulatory delay has harmed the patent incentive. Some new information sciences including computer software and genetic information are establishing new precedents in patent and copyright policy where progress is so rapid that

legal precedents are lagging behind the science.

Industry can and will support research in appropriate situations. As taxpayers, industries share the cost of government-supported basic research. Very large industries can afford in-house research and also award grants and contracts to research performers in universities and inconsulting laboratories. Associations of industries have banded together to support research in areas of common need. The Petroleum Research Fund, the Association of Pulp and Paper Industries, and the Electric Power Research Institute are notable examples. Although anti-trust law has inhibited industrial cooperation, it is clear that our steel, insurance, transport and selected other industries should be encouraged to cooperate in support of research in a manner which does not violate anti-trust law but helps our industry survive and serve the public more effectively.

Universities can work openly with industry utilizing the same grant and contract mechanisms used for government-sponsored research. Industry should not expect universities to engage in product development or research that is so applied that it does not contribute to our general store of understanding. While short-term, applied problem-solving may offer educational opportunity in fields such as statistics, computing and certain engineering areas, applied research is not suitable training activity for much of chemistry, math,physics and biology.

Universities should not engage in offering services or products in competition with industry. Most universities have specific policy statements regarding non-academic activities of their scientists. These policies can ensure that the university mission is fully served, that conflicts of interest are avoided or resolved and that students are optimally trained for their future careers. It takes leadership and vigilance to preserve openness of research, to bring its benefits to the public in proper return for their investment, and to resolve any real or perceived conflicts of interest. However, such efforts are necessary in order that university scientists preserve the public trust and confidence necessary for adequate support

of research and education at our institutions.

Although longstanding University of Wisconsin policies regarding allowable scope of outside activities and avoidance of conflicts of interest have served well, we have recently activated a faculty committee to reexamine these policies. We see a need for a better informed faculty and public regarding these policies. We are reexamining the new relations under which some faculty propose to play dual roles as faculty and as owners or executives of commercial enterprises. As universities explore whether such dual roles are compatible with academic principles, safeguards must be developed to preclude conflicts of interest and to assure the availability of information regarding financial support sources and contractual relations pertinent to research personnel, to funding agencies and other concerned participants.

In summary, industry can cooperate with universities and the government in a manner which is in the long term best interests of the nation. This cooperation should be by regular grant and contract mechanisms, free of restrictions on the right to publish in the scientific literature. Licenses for bringing patented discoveries to the public should be available to industrial sponsors who diligently pursue the development of the patent. Universities should be selective in accepting industrial contracts and focus on research which is basic or necessary for educating students in high technology fields. Our nation needs the new technology based on university research. A proper division of effort among the industrial, governmental and academic sectors brings the fruits of scientific research to the broadest public good.

Robert M. Bock - Biographical Sketch

Professor Robert M. Bock entered the University of Wisconsin after World War II, receiving a B.S. in Chemistry in 1949 and a Ph. D. in Physical Chemistry in 1952. He then joined the faculty of the University of Wisconsin at Madison where he is Professor of Biochemistry and Molecular Biology, and has authored over 100 research papers in the biochemical literature. In 1967 he was appointed Dean of the Graduate School and has served in that capacity since.

He has played numerous federal and international advisory roles. He was recently Chairman of a committee on the vitality of academic research for the National Academy of Sciences which, in 1980, published a report entitled "Research Excellence to the Year 2000", proposing innovative mechanisms to maintain a steady infusion of young scientists in University faculties despite problems of tenure density and declining enrollments. In 1981 he served as a consultant to the World Bank to review the Science and Technology Education Plan of South Korea. He is currently a member of the National Academy of Sciences' Committee to evaluate the quality of the research doctorate, and also serves on the National Research Service Act Biomedical and Behavioral Research Training Advisory Committee. He is Chairman of the Public Affairs Committee of the Federation of American Societies of Experimental Biology.

Mr. GORE. Thank you very much. If you would make those documents available to the staffs of the two subcommittees, I would ask unanimous consent that such among them as the subcommittees decide would be useful, contributions to the record be included at this point after review to determine which are appropriate to add to the record.

Our third witness on this panel is Dr. Roderic Park, vice chancellor of the University of California at Berkeley.

Welcome.

Dr. PARK. Thank you, Chairman Gore. I am pleased to be here.

My testimony is going to move from the general principles we have been discussing, after a few preliminary remarks, to some rather detailed policies that have been developed on the Berkeley campus and if there is interest, will be glad to give you some background for those.

For several years the University of California system has been involved in an energetic review of issues raised by the prospect of increased research cooperation between the university and private industry. While the impetus for this recent discussion has been the immediate issues posed by rapid advances in bioengineering, the review was also stimulated by continuing possibilities in microelectronics, agriculture and other important California industries. Two University of California systemwide reports have been developed, one on university/industry relations and the second on rights to intellectual property. Meanwhile, the Berkeley campus, in a cooperative discussion between the faculty academic senate and the administration, has developed a draft set of principles I will briefly describe this afternoon.

I believe the public may often misunderstand the impetus for recent policy discussions at universities on the topic of industry-supported research. One often reads in the press that universities are looking to private industry for funding to replace impending shortfalls in Federal research grants and contracts. However, from the point of view of a Berkeley administrator, this is a secondary consideration. The primary impetus for these discussions was the development of revolutionary techniques in genetic engineering at universities and research institutes over the past 10 years. The human resource behind these advances was, and remains, limited, and at least initially was largely located within universities and their associated research institutes. The possibilities of commercial exploitation of this new technology immediately became obvious, and venture capital, as well as established industry, began to woo the university and research institute experts with very attractive financial offers. These offers ranged from high consulting fees, to equity interest in new firms, to very attractive offers to leave universities and become private industry scientists, administrators, or both. The university was challenged to find the appropriate mode of relationship to private industry that reasonably accommodated both faculty and university interest so that we did not lose a generation of scientists to the profit sector. This challenge demanded that major research universities review their policies on university/industry relationships to, on the one hand, maintain the integrity of the institution in its traditional role of free inquiry, and on

the other hand to work cooperatively in rapidly advancing technological fields with industry. We firmly believe that these two objectives are completely compatible with the land-grant tradition, providing that carefully designed policies are followed. At the Berkeley campus of the University of California, our discussions on university/industry relations have entered around five topics: One, the nature of research done at the university; two, freedom to publish research; three, consistency with academic obligations; and four, confidential information exchanged with industry; and finally disclosure of financial conflicts of interest and review of nongovernmentally sponsored projects.

I'll take these up in order. First, the nature of research. As a teaching and research institution, the university must avoid the kind of work whose benefits to education and research are small; for example, routine testing of certain processes or products. The traditional values and standards of the Berkeley campus, embodied in graduate theses, published papers, and professional recognition of faculty members and students, are the best benchmarks for the kind of research that Berkeley pursues.

Freedom to publish research: Principal investigators and their graduate students should be free to publish any research results obtained from industry-supported work after no more than a minimum of time for patent licensing review or similar protection by the sponsor or by the university. It is totally incompatible with Berkeley's role as a leading institution of graduate instruction that publication of research be withheld beyond a minimum time.

Consistency with academic obligations: The primary obligation of faculty members is to the university. Faculty are expected to devote full time to their duties as researchers, teachers, and professionals. The ultimate standard is always the advancement of knowledge, the education and training of the students, and the welfare of the society which the university is bound to support. Review of compliance with this standard should be by academic peers which is the most reliable method for determining whether a research program is consistent with the faculty member's academic obligations.

In research projects that are funded by private industry, special care should be taken to insure that the benefits to the grantor provided by the university in exchange for financial support or other benefits do not result in the exploitation of its resources. For each contractor grant, the gains to the university, and to the public it represents, should be shown at least to balance or, if possible, to outweigh the services rendered to the grantor.

Confidential information exchanged with industry: Confidential information exchanged with industry that places restrictions on publication can rarely be justified on a university campus. Such projects should be carried out in industrial laboratories, preferably at a physical distance from the campus that makes interaction or consulting deliberate and not casual. Faculty members, within consulting guidelines, are free to participate in such confidential work. Graduate students, however, usually should not be included: progress toward their degrees depends upon their ability to publish, which confidentiality of the work will preclude.

Finally, disclosure of financial conflicts of interest and review of nongovernmentally sponsored projects: In California, the Fair Political Practices Commission requires that State agencies, such as the University of California, conduct an internal review of nongovernmentally sponsored projects to identify potential financial conflicts of interest. Financial conflict of interest in this case is defined as a compensation to the principal investigator, including gifts, exceeding $250 over the prior 12 months, from the firm to which the principal investigator is applying for a grant, a direct or indirect equity interest in the firm greater than $1,000 or a management position in the firm. It will not be assumed that the principal investigator who has a financial interest in the sponsoring agency will, on that account, be irresponsible in the conduct of university research. Our internal guidelines and expectations will be made known to faculty members whose proposals are identified, and followup peer reviews will be conducted to assure that the four prior principles are being followed. Finally, proposals for research grants from the private sector occasionally contain material relating to confidentiality or the direction of academic programs which require faculty review. A joint administrative-academic senate review committee will scrutinize such agreements and with the advice of the faculty, advise the administration in these cases. We believe the policies and administrative procedures outlined above are appropriate for maintaining the academic integrity of the research university and at the same time provide the indispensable transfer of university-developed ideas and technology to the private sector.

Thank you.

Mr. GORE. Thank you very much.

Let me ask a few questions before recognizing my colleagues.

Dr. Rosenzweig, you were involved in the planning of the Pajaro Dunes Conference. Since the issues discussed were so important, why were no observers from academic, industrial and government communities, or the President or anybody else invited beyond the immediate participants?

Dr. ROSENZWEIG. Well, a judgment was made, and it certainly was a controversial judgment and it may have been the wrong judgment, but the judgment was that we were prepared to trade off the value that would have come from some representation from the press for a somewhat higher quality, because less self-conscious discussion that we felt would emerge in the absence of particularly the press.

The number of people who could fit in the facility was limited. That was a physical limit and, as I say, it may in retrospect have been a wrong judgment. It certainly was a controversial judgment but that was the reason for it.

Mr. GORE. Well, that is a candid response.

In your statement you list some principals concerning the choice of research projects residing with the faculty who will do the research. Are you familiar with the Monsanto-University of Washington arrangement?

Dr. ROSENZWEIG. I know about what I have read in the press, essentially.

Mr. GORE. Well, at least one company official or company person on the committee must agree before any research project can be undertaken. It is a balance between four and four. Four from the university, four from the company, but five members have to vote for a research project before it can be undertaken.

Moreover, one of the four university members must be acceptable to the company before he or she is appointed with the caveat that the company cannot unreasonably refuse its approval. This matter would have to be resolved in court if there were a conflict, but the parties assume that if it ever got to court then the whole thing would break down, so presumably the company's refusal to accept one of the members would carry with it a considerable weight if both parties agreed that they could not afford to go to court.

Now, on that committee you have to have a vote of five in order to undertake a research project. Does that conflict with this principal that you say should guide the formulation of policy on such agreements?

Dr. ROSENZWEIG. On the face of it, I think it does. That clearly is one of the more controversial elements of that contract, as I understand it. I think there is probably a more fundamental reason why in practice it will turn out to be a good deal less troublesome than it may seem to be on the face of it.

If you back up a step, it strikes me that a company like Monsanto invests in research in a university primarily because the scientists they are going to support are doing, and are expected to continue to do high quality work in a field of commercial interest to the company. I assume that is true in the Washington University case.

In that case, as you say, proposals originate with the faculty, as I understand it, or in response to requests for proposals from the committee and they are judged by eight persons on the committee.

The question is, what criteria will the committee use and the fear, I guess, is that those criteria will be unduly influenced by Monsanto's commercial interests. Well, maybe so, but if the Monsanto people are as sophisticated as I think they are, they are going to define their interests broadly enough to encompass the best work that is coming out of the department being supported.

And that is why I think that in practice they are going to wind up supporting what the faculty wants to do because that is the way you get good work out of faculty. In any case, the outside review that takes place after 3 years, I think should help us to know how it is working.

I think while it might not be an arrangement that I would want to negotiate myself from my own institution—I don't make that judgment—I hold that out as a possiblity; I don't see it as being so intrinsically wrong that it can't stand there to be evaluated and to be learned from.

Mr. GORE. Well, I hope you are right. I was impressed by the amount of time that both parties to that agreement spent in analyzing and thinking about the problems inherent in such agreements. I was impressed also that some problems were resolved in a way that left such questions wide open still after the agreement.

You and I have talked on many occasions and I agree with the tone of your statement that the amount of attention being paid to this subject should not be criticized by comparing it to the lack of attention to previous developments in the research community.

Perhaps the previous agreements did not get sufficient scrutiny and I think, moreover, that it is important for the university community and the business community to be sensitive to the implications of this new alliance. The questions which society as a whole is likely to confront as a result of this accelerating scientific revolution without precedent in the history of the world are so difficult and so compelling that the forum in which those questions first arise should be sculpted with considerable care. The sensitivity arising from that endeavor might carry over into the initial reactions to these questions that are going to be so difficult for society to resolve.

Dr. ROSENZWEIG. I think you and I agree on that entirely, Mr. Chairman. My problem is with people who approach these questions out of two premises. One of them is that the influence of business is so painful, not to say evil and the conduct of university faculty and university administrations is so innocent, not to say complicit that one hardly even has to think about how to deal with these questions.

You deal with them in direct comprehensive regulatory style. I just think that is a mistake. I don't think we know enough. I think we would stifle the emergence of lots of interesting possibilities that we can't foresee now and I don't think that the record justifies either of those premises.

Mr. GORE. Yes, sir. Moreover, people in the university community should not get so wrapped up in fighting the cartoon-like image of those raising such questions as to miss the underlying importance of the questions themselves.

Dr. ROSENZWEIG. I agree with that, too.

Mr. GORE. Dr. Bock, you have had three researchers at your university associated with high technology companies, biotechnology companies, at least three. Two of them, Dr. Timothy Hall and a Dr. Kemp were associated with Agrigenetics and because of a perceived conflict were required by their departments to take a leave of absence from the University of Wisconsin. A third, Dr. Winston Brill, who testified before this subcommittee a short time ago, was associated with the Cetus Corp. and was the head of a third department at the same university and yet was allowed to stay.

Now, the distinction between those cases is what I am interested in. Was it the result of no university policy or rather a policy that leaves the discretion to the individual department. Was it because of the corporations involved, the individuals involved or because of the fact that Dr. Brill happened to be the head of the department making the decision in his case?

Dr. BOCK. Well, Dr. Brill has never been the head of the department of bacteriology.

Mr. GORE. I apologize for the mistake.

Dr. BOCK. I wanted to correct that point.

Mr. GORE. Well, make the distinction for me.

Dr. BOCK. I think my answer to your question is fairly close to all of the above. Dr. Kemp was an employee of the U.S. Department of

Agriculture and Federal rules said he could not work for private industry while continuing in that employment, so that was a direct Federal requirment. He was a USDA employee full-time, based in a USDA plant development lab at our university, a very welcome, excellent scientist. He could not engage in activities with a commercial company while remaining a Federal employee. He was not a university employee.

Mr. GORE. Oh, I see. Well, our testimony yesterday was a little difficult to understand on that point.

Dr. BOCK. He was a faculty member directing graduate students as a longtime career Federal employee, welcome to our campus.

Mr. GORE. Well, that is a little complicated, then. I see.

What about Dr. Timothy Hall, he was not a Federal employee; was he?

Dr. BOCK. That is right. Dr. Hall has gone on leave of absence and has proposed to the Department of Horticulture a division of activity and effort which he feels would fully satisfy his performance and requirements as a university faculty member and would still permit him to be a research director for the Agrigenetics Corp., a fine laboratory in Madison, Wis.

His department has his proposal under consideration and has not found that they are satisfied with the separation of efforts and removal of possible conflict to the point that they are willing to activate and make permanent the proposed arrangement. In the interim, he is on leave of absence. He has been invited back by other departments as an adjunct professor to participate in academic activities but not primarily as a faculty member in the Department of Horticulture.

This is a legitimate decision, a responsibility of that department and its chairman to judge whether the specific proposal for division of activity, conduct of research and outside responsibility is compatible with the mission of that department.

I might mention that that department has had as its principal mission throughout its history the service to the individual family farmer. It is an extension based department which has never taken compensation for such service and therefore grown up in a tradition of service to the family farm.

That practice is changing rapidly as agribusiness is replacing much of what used to be our family farm. In fact, our productivity in the State of Wisconsin is primarily no longer coming from the traditional family farm.

In the case of Professor Brill, he was a professor in the Department of Bacteriology, a department which is world famous for having developed not only the culture production of penicillin, but drug after drug and pharmaceutical after pharmaceutical from bacterial fermentation processes.

They have designed many of the sewage and waste treatment facilities that are in place around the nation and have served industry wisely and well and now know how to do it comfortably while still training excellent graduate students and conducting their research openly.

They had a tradition of service. They knew how to do it and felt comfortable. That was a completely different environment. That department chairman examined the proposed division of activities

and of topics of research (which were different in the two cases) and with the advice of his faculty determined that they could go ahead and continue the proposed arrangement on a temporary basis.

The Department will examine the results and the performance to assure that the university mission is fulfilled and that there are no conflicts of interest that become apparent as one gains experience.

We have activated a university faculty committee to study the process and the problems of such a dual role. This can be a difficult role. In a case under discussion last week, the faculty member immediately decided to sever his connections with the university but said that he would hope that we would welcome him back as a special lecturer or visiting professor if the occasion permitted.

He did not even ask the dual role question. He immediatley decided to sever his connections. The university policy was followed in all three of these different cases. The resulting decision was different because the situations were different.

Mr. GORE. Mr. Walker?

Mr. WALKER. Thank you, Mr. Chairman.

I understand a recent article in Chemical and Engineering News suggested that more faculty members are thinking of unionizing. Could anybody give me anything to which they might attribute that kind of a trend?

Dr. ROSENZWEIG. I am not sure that is true. The California State college and university system, not the University of California system, the CSU system did recently vote for unionization but my impression is that the movement toward faculty unionization has slowed somewhat in the last few years rather than accelerated and the CSU case is the leading example to the contrary. I believe that it is an exception.

Mr. WALKER. Does increased commercialization encourage such activities, in your opinion?

Dr. ROSENZWEIG. No, not markedly, I would not think. The places at which most of the research which is of interest to business is taking place are the institutions that are probably least susceptible to unionization.

Mr. WALKER. The president of Harvard has recommended some guidelines for universities accepting industry funds without compromising academic goals. He set out the following:

> Denying exclusive licenses or university patents in which a researcher has a significant interest. Prohibiting a professor from holding stock and getting research grants from that same company. Forbidding professors to hold large amounts of stock in companies that might benefit from that professor's research and a university should not accept partnership in the formation of a company that involves university professors as company officers.

Would you agree with those guidelines or would you add anything to those guidelines?

Dr. BOCK. I would agree with the objectives of those guidelines but I believe there are solutions that are better than the specific guidelines suggest. Our university conflict of interest rules require the identification of such circumstances and then an authority above the individual involved must hear a proposal for how that conflict of interest will be resolved. A typical resolution is, (a) make it public. Make sure that everybody involved knows of the situa-

tion. (b) Remove all decision authority regarding those specific interactions from the persons who might be in conflict of interest. In such instances a committee, an outside body, or a peer review group becomes the decisionmaking body. This is exactly parallel to the way we have handled our nepotism rules which in the past denied opportunity to spouses of our faculty and now open more equitable opportunity be providing that decisions regarding that spouse are completely removed from the authority of the other member of the family.

Mr. WALKER. Dr. Park?

Dr. PARK. I would like to comment on that briefly. As I mentioned, we have a requirement for disclosure. It does not prohibit a person from having a potential conflict of interest but the conflict of interest, the potential one is then very closely monitored to make sure that the university standards are being met.

I think an example of the difficulty with writing down specific rules is that it is a very different thing to own maybe 50 shares in IBM and consult for IBM and at the same time own 10 or 20 percent of a small venture capital outfit. I think that is the real problem one has to address.

Mr. WALKER. That is the struggle that we have wrestled with around Congress, too, many of the ethical questions as to whether or not disclosure is enough or whether or not you have to define specific guidelines over which members of Congress, or in this case the university professors, shall not step.

So it seems to me that we are in very similar kinds of negotiations when it comes to setting those kinds of roles.

Dr. ROSENZWEIG. My guess is that neither of us has found wholly satisfactory solutions to the problem.

Mr. WALKER. I think that is right. I know it is true here. I can't speak for you.

Thank you, Mr. Chairman.

Mr. GORE. My cochairman, Doug Walgren.

Mr. WALGREN. Thank you, Mr. Chairman.

I apologize for coming in late. I wanted to ask Dr. Rosenzweig; in your testimony you indicate that the change in universities with the onset of substantial Government funding was a major change. I am sure it was and certainly it would overshadow anything that you feel we are experiencing today.

And yet, don't you feel though that the kinds of conflicts of interest that might arise out of commercial involvement are a more direct threat to the intrinsic nature of the university than would be funding from a relatively neutral source, and in that sense are not we dealing with a different kind of possible conflict?

Dr. ROSENZWEIG. Well, I guess you are asking my opinion on that and my opinion is that nothing is likely to come out of the relationships between universities and business that is so threatening to the fundamental values of universities as was, for example, the widespread conduct of classified research on campus, as were the loyalty oaths that accompanied various government programs in the earlier years of Federal support.

Those were very, very difficult issues which universities took a long time to work through with the Government, and that posed, I

think, fundamental challenges to what universities had traditionally stood for.

I don't see anything of that magnitude coming out of this set of relationships, which is not to say that there are not problems and that there are not going to be additional problems that are going to be troublesome and difficult to work through.

But I guess I just think that what accompanied the Government support of research in universities was of such extraordinary magnitude and such profound effect on the nature of these institutions for good and for bad that what is happening now is small compared to that.

Mr. GORE. Will my colleague yield?

Mr. WALGREN. I yield.

Mr. GORE. Our two subcommittees had hearings earlier this year during which Adm. Bob Inman testified about his suggestion that universities figure out a way to structure a right for the Government in the national security apparatus to review sensitive scientific research.

He said during those hearings that one of the reasons it occurred to him that the time was ripe for such a suggestion was the perceived willingness of universities to grant such review rights to the sources of corporate funding. Indeed, the cryptology agreement is not very different from the Hoechst-Massachusetts General agreement or others similar to it.

So it seems to me there is a connection between the two and while one might have thought that the answer to those questions from another era had long been accepted, in fact the question is being raised again.

Dr. ROSENZWEIG. I think Admiral Inman was essentially incorrect on that particular part of his remarks. Most institutions that I know of, certainly our own institution, deal with publication review by government and by industry in an even-handed manner. We permit a limited time for review of publications but with the final decision on whether to publish residing with the scientists.

Mr. GORE. That's what the cryptology agreement is; in essence.

Dr. ROSENZWEIG. Yes, that is correct.

Mr. GORE. Do you think that agreement is OK?

Dr. ROSENZWEIG. I think it is too soon to say whether that is okay. The cryptology agreement is different from the ordinary run of such agreements because it is not, and excuse me for getting into the more technical details, it is not monitored by the standard contract monitors the way many government contracts are, but by a separate committee.

There is a serious question of whether that model is extendable at all beyond the field of cryptology, which is very small, very specialized and does not produce a whole lot of material. That agreement itself was thought of by its creators as experimental and the experiment has not been judged yet. The evidence is not in yet.

Mr. GORE. I thank my colleage for yielding.

Mr. WALGREN. Dr. Bock, I understand that you are involved in relatively large scientific societies. My question is whether or not the larger societies are thinking about guidelines and codes that could be developed within their professions that would be helpful in resolving the conflicts here.

99-177 O - 82 - 9

Dr. BOCK. Well, certainly the American Society of Microbiology has among its membership, I believe, a majority of industrial commercial members and the academic community is not the majority. There are a very substantial number of members of the federated societies of experimental biology that are in industry or private laboratory settings.

They have not brought this topic up as a topic of concern. In fact, the societies that are the best acquainted with it and have the longest experience with it along this line are the least concerned. I think that if you look in the engineering profession, the various American engineering societies, you will not see a ferment about a new revolution in university/industrial relations.

Furthermore, if there is a ferment, it is the expectations of our States and our Government and our industries that each wants and needs help to survive in a world economy. They need this technology transferred to them effectively and rapidly and we are being asked to respond.

Mr. WALGREN. In those societies there has not yet been any working group trying to evaluate manpower demand.

Dr. BOCK. There has been an attempt to evaluate the manpower demand, in fact, the National Research Council has asked for help from professional societies in documenting what fraction of their Ph.D. research manpower is now going into the commercial sector so that they can better predict the future manpower needs. We are just beginning that task and plan to have a report within a year as to whether this is large enough that it would compete for the manpower pool for basic research in the health and biomedical sciences.

Mr. WALGREN. Is there any distinction that should be made between the outreach between industry and university in engineering and that in the biotechnology areas where you are really talking about a breakthrough in commercializing it in a discreet fashion?

Dr. BOCK. I think there are a couple of distinctions. One, I believe it is widely agreed that one cannot train good engineering researchers without realization of what the marketplace is and what the activities in industry are so it has been a long term tradition that engineering faculty contacts with industry has a positive role if controlled, if reported and if carefully administered.

It has a positive role on the nature of the research. It is too early to tell whether these types of relations will develop within biotechnology. We are essentially reaping the benefits of at least 20 years of intense exploration of new frontiers in biology. (The understanding of the nature of the gene, its expression and its regulation.) We have gained new tools. In the past we had to take what nature gave us in selecting an organism or a tissue that expressed a particular desired product.

Now we can put the valves in place where we want them and turn them on and off when we want to. This is a very new technology so we are learning very rapidly.

Mr. WALGREN. But would those two different areas raise different threats to the traditional university student relationships that we know of?

Dr. BOCK. I don't believe that the difference is of a great magnitude. I think the lack of experience in the biotechnology is a funda-

mental difference, although we do have substantial experience in the fermentation and the pharmaceutical industries which are the principal performers in the new biotechnology.

Mr. WALGREN. Would you like to comment, Dr. Park?

Dr. PARK. I think there is difference between the traditional university-industry relationship in the engineering college and what happened over the last few years in biotechnology, but I think every indication is that the biotechnology area is rapidly going to move into the engineering direction.

Many industries are developing an in-house capacity to do genetic engineering. They are not going to be wooing the university to quite as great an extent we experienced over the last several years. The thing that was remarkable about biotechnology was that is initially resided totally within universities and institutes and when industry became aware of its importance they had only one place to go in order to get the human resources to help them out, and that's what put on the tremendous pressure.

As they develop their own in-house capacity, I think we will find biotechnology moving in much the same direction that engineering has traditionally.

Mr. WALGREN. It seems a little different in my mind in that in the engineering area the university is in trouble and is reaching out to use and deliver almost gene machine training to its students in the process, whereas in the biotechnology area, although I am sure there are parallels, it is certainly not the university that is in trouble at least as to the resources at that point or the idea. The university has the idea completely within its grasp and it is the industry that is pulling the strength away from the university and perhaps jeopardizing some of the relationships and I just wonder if that is significant.

Dr. PARK. I think you are correct. If we made a comparison, let's say of last year or the year before and looked at those two areas, our engineering colleges really need industry to help and support them and on the other side in the biotechnology area, it was these new venture capital outlets and huge chemical companies that needed the university. It really was the shoe on the other foot for that brief period of time.

Dr. BOCK. I might comment that we have seen this imbalance in demand and available manpower in other fields. Computer software is currently in the same state as biotechnology. We are having very great difficulty competing with industry because their demands are great for the same people that we need to teach our students. This has happened as areas of rapid development in engineering, as areas of new technology emerge and become attractive.

So it is a phase that we are going through. Engineering has cycled up and down in these phases for generations. I suppose that biotechnology will begin the down cycle fairly soon.

Dr. PARK. We hope so.

Mr. WALGREN. Thank you, Mr. Chairman.

Mr. GORE. Let me ask a couple of more questions and then I will have to leave for an amendment on the floor.

Dr. Rosenzweig, the Washington University-Monsanto agreement that you heard about yesterday calls for a committee at the univer-

sity to provide guidelines on what the researchers can say about their work.

The concern of the company is that foreign patent laws are more difficult to comply with if there has been a public disclosure or divulgation to use the correct term. What is your opinion concerning restrictions on the ability of university researchers to say anything or to say very much about what their work involves at a conference or symposium, for example, in order to assist the company to get worldwide patents, perhaps even after the American patent has been secured.

Dr. ROSENZWEIG. If you don't mind, I would like to take my response out of the context of the Washington University-Monsanto agreement because I don't know that in detail.

Mr. GORE. Fine.

Dr. ROSENZWEIG. I am happy to comment on the general problem because it is a more general problem. I think it is a very troublesome matter for extensive delays in scientific communications to take place in order to protect patent positions.

Mr. GORE. Verbal or written?

Dr. ROSENZWEIG. Yes, sir, that is correct. That is not necessary in order to protect American patent rights and it may be that institutions and scientists—the impulse does not always come from the university administrations or from businesses—that institutions, scientists and businesses will have to consider foregoing some portion of their patent protection in order to protect the process which produces the innovation that is of value to them.

Mr. GORE. Well, Washington University is, to bring it back to the specific, willing to accept such guidelines. They have signed their agreement and presumably that willingness is a new one which results from corporate funding. Is that not a fair assumption?

Dr. ROSENZWEIG. Well, I don't know the history or circumstances of that agreement.

Mr. GORE. Well, you said a moment ago that Admiral Inman was wrong in perceiving a new willingness by universities to consider restrictions of this sort. There does seem to be some evidence of that.

Dr. ROSENZWEIG. I think in fact there is a more serious problem than that that's posed by the patent situation and that is the treatment of material that is not patentable but has proprietary value and I don't think any of us has faced up very squarely to that question.

Mr. GORE. Well, let's just stay on the specific case of the patents for a moment. Would not you agree that there is evidence that universities are more willing to accept restrictions of this kind that they were not willing to accept in the past?

Dr. ROSENZWEIG. No.

Mr. GORE. What do you make of the Washington University willingness to accept that restriction, then?

Dr. ROSENZWEIG. There are other instances of it that predate that agreement. It has always been the case that scientists have different communication styles. Before there was any question, molecular biology, remember, until the last few years was the purest of the pure.

High energy physics had nothing on the biologists in terms of the purity of their motives and their lines of inquiry and yet scientists in some laboratories were quite open about their willingness to communicate what they were doing and scientists in other laboratories for reasons having to do with their personality structures, or their desire to protect the possibilities of Nobel Prizes, I don't know what motivates all those people in all those circumstances, were not very communicative at all.

It is not clear to me that anything new has been added by virtue of the commercial applications although it may be that the extent of the unwillingness to communicate has increased some. I don't know. I hear stories but I don't see much evidence.

Mr. GORE. I see. Well, I applaud your willingness to consider and discuss the philosophical implications that are raised by these new developments in the abstract. But the way you seem to minimize the occurrence of actual problems seems at times to extend even to a denial of the fact that these problems really are occurring and that there really is a change in the way universities are looking at these questions.

Dr. ROSENZWEIG. My impression is that so far the arguments are largely hypothetical.

Mr. GORE. Well, they are not at Washington University, are they?

Dr. ROSENZWEIG. Well, nothing has happened yet, has it. Let's see what happens.

Mr. GORE. Well, as the fellow falling out the 10 story window said to the person on the fifth floor, "so far so good."

Dr. ROSENZWEIG. They just barely entered the room, Mr. Gore, they have not even entered the room yet.

Mr. GORE. OK.

Dr. Bock, your distinction between the two cases of Dr. Hall and Dr. Brill was a little unclear to me. You seem comfortable with the fact that the circumstances are so different that while one person can stay with the university and can still be the director of research for a private corporation, the other fellow, because he had a position with another corporation, had to leave.

You seem comfortable that the circumstances are easily distinguishable. Can you tell me specifically what is it about the two cases that distinguishes one from the other. It is not just the totality of the circumstances including the personality of the individual. There has got to be some specific distinction.

Dr. BOCK. Could I comment on the patent situation just before I answer this question?

Mr. GORE. Sure.

Dr. BOCK. I believe that, in fact, universities are learning from each other that 90 days is long enough to accomplish patent filing and they should not hold anything back for over 90 days because otherwise your patent attorneys are under little pressure to be prompt. In the past, universities might have been more liberal and given 6 months or a year for a leisurely filing.

I believe that they are getting harder nosed and insisting on prompt action as they communicate with each other. But in the past, some short, reasonable time was allowed. I believe, there is a national awareness that there is a worldwide competition for high

technology trade and that it is our duty to process foreign and domestic patents. I must say that some current Federal agency policies are threatening our ability to get foreign patents. I will be jawboning these agencies to try to get that corrected because I think that they are endangering our ability to get foreign patents at all because of their way of responding to the Freedom of Information Act.

Now, on the two cases that were concerned.

Mr. GORE. Briefly, if you could.

Dr. BOCK. The onus is on the individual who is engaging in the outside activity to propose a resolution for conflict of interest. And the proposals from Professor Hall and from Professor Brill were distinctly different in the topical separation of research activities so that in one case there was no overlap in the topic of what would be researched by his graduate students at the university and what would be researched in industry in his other role.

In the second case, I believe that the chairman was unable to find that distinction and thus ruled that he was not satisfied that conflicts of interest had been appropriately resolved. Yet the onus is on the professor.

Mr. GORE. Fine.

So the distinction is that in one case Dr. Brill was conducting research at the university that was completely different, at least for the time being, from what he was doing with the company and in the other case there was an overlap between the two topics. It is a rational distinction, it seems to me.

One final question.

Dr. Rosenzweig, you raise a very important issue and in my eagerness to pursue this other point, I passed it over and I want to come back to it now. When you talked about all that body of knowlege that is somewhat proprietary in nature or could be so considered, yet it is not patentable. We take for granted that university researchers and professors publish their work today.

In fact, for years there has been the criticism of the "publish or perish" rules at many universities.

Is it likely that the most pronounced effect in some of these cases will be that university researchers simply will stop publishing so much and stop making public so much of this work?

Dr. ROSENZWEIG. I think we are going to have to be very careful to see that that does not happen.

Mr. GORE. Well, it would happen quietly, would it not?

Dr. ROSENZWEIG. But it would not be invisible, I don't think. I think it would genuinely be a tragedy if that were to happen. I think that individual scholars, professional societies, university administrations, Government agencies, if you will, have a very high obligation to be alert to the possibility that that might happen, and, from the point of view of universities at any rate, to be quite prepared to forgo certain kinds of commercial advantages and certain kinds of financial advantages I should say coming from commercial arrangements if it appears that that is a consequence of particular arrangements.

I don't find that hard to deal with at all from the university's point of view.

Mr. GORE. OK, thank you very much.

I have an amendment on the Floor, I will be back.

Mr. WALGREN. It seems to make sense to take a brief recess at this point. I would like to take up a matter on the Floor. It won't be 10 minutes.

Dr. ROSENZWEIG. Would you like us to come back, Mr. Walgren, or are we finished?

Mr. WALGREN. No, this is a good break for you. Your participation has been appreciated and you are excused.

We will recess. [Recess.]

Mr. WALGREN. Let's call ourselves back together. I apologize for the break, but there are too many fish that have to be fried around here.

So I hope it wasn't too uneventful for you.

On the second panel, we will hear from Dr. William Raub, Associate Director for Extramural Research and Training for the National Institutes of Health and Dr. Donald Senich, Director, Division of Industrial Science and Technology Innovation, National Science Foundation.

We are pleased to have you both before the committee. You have appeared here before. The committee has been appreciative of your contributions. The Foundation, of course, has made a great contribution to a healthy climate for university-industry cooperative research in many areas and we know the NIH record in this area has been strong.

Your written remarks will be made part of the record. You can proceed to summarize or outline your presentation as you feel most effective. Let's start with Dr. Raub.

STATEMENTS OF DR. WILLIAM F. RAUB, ASSOCIATE DIRECTOR FOR EXTRAMURAL RESEARCH AND TRAINING, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND DR. DONALD SENICH, DIRECTOR, DIVISION OF INDUSTRIAL SCIENCE AND TECHNOLOGICAL INNOVATION, NATIONAL SCIENCE FOUNDATION

Dr. RAUB. Thank you very much, Mr. Chairman. I have a brief statement that I would like to read.

Thank you for giving me the opportunity to represent the National Institutes of Health [NIH] at this hearing on commercialization of biomedical research. As you and the other members of the subcommittees know, this subject has generated immense interest throughout the scientific community, and especially in biomedicine where there are myriad issues to consider involving science, health, ethics, economics, and law. I will concentrate today on only the major issues and responsibilities that, under law and regulation, directly affect the NIH and its mission. I also will bring you up to date on NIH activities related to this subject that have taken place since I testified before these subcommittees a year ago.

The fundamental mission of NIH is to foster biomedical research so as to improve human health and well-being. The emphasis has been, is now, and will continue to be on basic research, for without new knowledge the weapons against illness will remain only partially effective. But we are concerned with the entire continuum of

biomedical inquiry, including its applied aspects: at the bedside, in subserving regulatory and other policy decisions, in eliminating harmful environments, and in promoting healthy life styles. The ultimate goal of our research, of course, is the prevention of disease and disability.

In carrying out the NIH mission, we have developed a sound relationship with the academic community, mainly through the grant mechanism. We also have developed good ties with industry, primarily through the contract mechanism. We are convinced that the current system for funding biomedical science is productive; its benefits are flowing to the general public as never before, and the prospects for even greater payoff are bright.

A notable example of success through this triangular partnership is the newly licensed virus vaccine to combat hepatitis B, a debilitating liver disease. The first breakthrough came in 1965 through NIH-sponsored basic research. Subsequently, scientists in Government and academia were joined by their peers in industry to develop the vaccine approved by the Food and Drug Administration (FDA) last November. In announcing licensing of the vaccine, FDA Commissioner Arthur Hull Hayes highlighted this three-way cooperation, as he noted that this vaccine is the first completely new viral one in 10 years and the first ever licensed in the United States that is made directly from human blood.

Hepatitis B is a major public health problem in the United States; there are 200,000 to 300,000 new infections annually, 100 to 200 deaths from acute hepatitis each year, and a reservoir of 400,000 chronically infected carriers, many of whom continue to transmit the disease. The Centers for Disease Control estimates the cost of hospital treatment alone for hepatitis B (the minimum amount that can be saved by using the vaccine) at about $4.3 million a week. With your permission, Mr. Chairman, I will submit here two documents for the record: an NIH publication that chronicles this remarkable story and the statement by Dr. Hayes to which I referred earlier.

Mr. WALGREN. Without objection, they will be made part of the record.

Dr. RAUB. Thank you, sir.

These subcommittees have been the vanguard of congressional interest in the scientific developments and economic forces that, in recent years, have placed increased pressure on all three members of the Government-university-industry triad. Universities are seeking new sources of funding at the same time that industry is perceiving new economic potential from biomedical research, and the emerging array of new forms of corporate cooperativeness between universities and industry are causing the Government partner to reexamine its role.

In that context, Mr. Chairman, and with specific reference to Public Law 96-517, we see a threefold role for NIH: continued fostering of biomedical research in universities, hospitals, not-for-profit research institutes, commercial organizations, and Government laboratories and clinics; promotion of rapid and responsible technology transfer for public benefit, both through NIH programs and through the encouragement of university-industry cooperation;

and protection of the public interest in the results of its substantial investment in biomedical research.

While NIH is prepared to assist universities and commercial organizations to strengthen their interrelationships, we do not view our role as a central one. The issues prompted by some of these joint ventures, we believe, are primarily matters of university governance. But, to the extent that Federal funds are involved, we of course, will strive continuously to insure that the public interest is being served appropriately.

I now will summarize some of the activities related to commercialization of research in which NIH has engaged since last summer.

We have examined in detail the provisions of the new patent law, Public Law 96-517, and its implementing regulations; this work was carried out both internally and in concert with members of the NIH Director's Advisory Committee and its Working Group on Cooperative Research Relationships with Industry. We have carefully considered such issues as patent rights, protection of proprietary information, and implications for peer review of research proposals. Based on these considerations, we are now drafting guidance for NIH grantees and contractors which will clarify their responsibilities and the rights of the Government under the patent law.

During the previous hearing on commercialization and subsequently, this subcommittee expressed specific interest in the agreement between Massachusetts General Hospital and Hoechst AG. At the invitation of MGH, a team of staff members from the Department of Health and Human Services [DHHS] met with representatives of the hospital to assess the contract and clarify any questions raised by either group. In brief, Mr. Chairman, we underscored the applicability of the patent law and regulations to any inventions or products arising from that endeavor, to the extent that Federal funds contributed directly. The MGH officials demonstrated that they understood their responsibilities and assured us that they intended to comply fully with the law and regulations. We came away satisfied that the Government's rights and the public interest can be protected adequately under the MGH-Hoechst agreement. With your permission, Mr. Chairman, I will submit for the record a copy of the NIH minutes of the site visit to the MGH.

Mr. WALGREN. We would like to have that as part of the record.

Dr. RAUB. Thank you.

We are ready to engage in similar discussions with other NIH grantees or contractors who have made, or are contemplating, similar arrangements with private industry. We believe that such information exchange well in advance of any inventions under these joint ventures will do much to prevent discord or other difficulties when results of potential commercial interest begin to emerge.

As part of an overall refinement of our internal procedures for review of research reports from grantees and contractors, we are improving our system for handling invention reports. The goals are to make certain that invention reporting is both accurate and timely and to detect areas where improved guidance may be needed. Also, we have informed our staff and awardees on the provisions of patent law and regulations.

We also have taken several actions to encourage industry—especially small business—to participate in NIH research and development programs.

We recently intensified our efforts to identify small R&D firms with expertise and interests in biomedical science. We are asking such firms to provide resumes of their capabilities. We are also encouraging their participation in regional meetings (cosponsored by the Small Business Administration and the National Science Foundation) whereby they can learn about Government programs in areas of mutual interest.

As of January of this year, for-profit organizations became eligible for grants from the DHHS. Accordingly, we are advertising that fact and also are requesting nominations of additional scientists from the for-profit sector to serve on our peer review groups. Although private sector scientists have participated in these committees for several years, we believe that we should enlarge the number of reviewers who have had first hand experience in such settings.

We hope that commercial organizations, especially small businesses, will be responsive to these NIH administrative initiatives. We believe that important R&D opportunities exist for them, especially with respect to the development and application of diagnostic and toxicity tests.

In the area of technology transfer, Mr. Chairman, our Office for Medical Applications of Research is the focal point for special efforts to translate the results of biomedical research into the practice of medicine and public health. In particular, this office coordinates technical consensus activities at NIH. In this process, biomedical researchers, practicing health professionals, and others, including representatives of industry, are brought together to exchange information and opinions on the suitability of a specific health care technology for general application. The object of consensus conferences is to explore publicly the scientific background and key issues pertaining to the technology under consideration and to seek a consensus among participants concerning its use, safety, and efficacy.

Mr. Chairman, we hope this discussion of NIH views and activities regarding commercialization of the results of biomedical research and our summary of recent actions relative to Government-university-industry research cooperation will prove useful in your deliberations.

I will be pleased to respond to any questions you may have.

Mr. WALGREN. Thank you, Dr. Raub, very much.

Dr. Senich, we will go right into your presentation.

Please feel free to summarize or outline in whatever way you feel effective.

Dr. SENICH. Thank you, Mr. Chairman I am pleased to report to the committee the National Science Foundation's experience in fostering university-industry cooperation in biotechnology research. Accompanying me today is Dr. Robert Rabin, the Deputy Assistant Director for the Directorate for Biological, Behavioral and Social Sciences.

I would like to note at this point that the Foundation and the National Science Board have been examining issues related to in-

dustry/university cooperative research and will issue a report on this subject later this summer. The foundation currently does not have a large number of university-industry cooperative research projects or programs in biotechnology. We do have efforts to increase knowledge in areas of biotechnology and to encourage university-industry coperative research. Programs of support for research in biotechnology are included in the biological and marine and material sciences, as well as engineering research efforts. These two efforts are converging and I certainly expect more cooperative biotechnology research in the near future.

The Foundation's Industrial Science and Technological Innovation Division is exploring and evaluting several strategies for industry/university cooperation. I would like to briefly describe three programs most involved in these efforts.

First, the industry/university cooperative research projects program has been operating since 1978. Its objective is to strengthen cooperative science and engineering research on specific problems or issues of mutual interest to university and industrial scientists. Research proposals are prepared and submitted jointly by academic and industrial institutions. To insure the high technical quality of the proposed research, all proposals are subjected to the same high standards of peer review as those addressed to the traditional research directorates at NSF.

Further, as in all NSF research, the results of research from this program are intended for publication in the scientific and engineering literature. NSF always pays for the costs of university research in these projects. In about one half of the projects, the firm (or firms) covers the cost of its own participation. For the rest, NSF provide some limited funds to cover industry costs. It is current policy that NSF will pay only up to 50 percent of the costs of the industrial participant except for small businesses, which may receive up to 90 percent of their costs. We believe that requiring a firm to pay a signficiant portion of its research costs insures that the proposed research is considered a priority item by the firm's management. NSF funds are not intended to substitute for funds the firm would normally commit for research but provide for expanded cooperative research programs with universities.

On the basis of a recent empirical assessment of the program, it is clear that the program is attracting high-quality researchers from prestigious universities and technolgy-oriented companies. The amount of interaction between university and industrial scientists is significantly enhanced by the program since about two-thirds of the academic participants have had only limited consultant or employment relationships with their firm partners. A copy of that report, sir, I believe, has been submitted to your staff. This assessment is described in interim report 1, "Descriptive Analysis of Projects 1978 to 1980, Assessment of the Industry/University Cooperative Research Program."

Mr. WALGREN. Thank you very much.

Dr. SENICH. The second program is the university/industry cooperative research centers program initiated in 1973. Its purpose is to increase knowledge in technological areas of mutual concern to universities and industry. NSF provides support for only the initial development of these centers. NSF and industry's support in initi-

ating a center provide for a broad-based research program, one large enough to be of interest to industry but too large and diversified for any one company to undertake alone. Each center develops its own character as determined by the principal investigator, the university policies and objectives, and the potential corporate sponsors. All centers are expected to increase the industrial support for their research program as NSF support is phased out within a period of 5 years or less. A center is considered a success when its research funding is at least at its original level, but no longer dependent on NSF support.

Six industry/university cooperative research centers are now in operation, with one, the MIT Polymer Processing Center, already self-sufficient. In fiscal year 1982, we expect the total budgets for these centers will approach $6 million with industry providing about $4.5 million. The industry/Government cofunding ratio of 3 to 1 for the centers program clearly denotes the catalytic effects of federal funds.

I should note that we are also assessing this program. One of the products of that assessment will be a practice manual, or "cookbook," on establishing and operating a center.

The last program is NSF's small business innovation research program which was started in 1977 to encourage quality proposals from small businesses to NSF. I know that you are aware of this program, so I will be brief in my presentation.

This program has three phases. In phase I, proposals are invited from small firms in areas of research interest to NSF and are peer reviewed by normal NSF procedures. Successful proposals are supported for up to 6 months to study the feasibility of various scientific or engineering approaches to technical problems. At the end of phase I, those studies considered most likely to benefit by continuing support are eligible for phase II awards. Proposals for phase II, whose purpose is to verify the soundness of the research approach, are again subjected to the normal competitive peer review process. Phase III is to pursue commercial applications, from the phase I and II results and is to be funded entirely by private capital sources.

This program provides an incentive for the grantee to pursue commercial applications based on the research results. Proposers are encouraged to develop cooperative arrangement with university resources and most grantees have used university researchers as consultants or subcontractors for specialized activities.

All three of our programs have become involved in biotechnology. The industry/university cooperative research projects program has funded a number of projects linking together firms and universities such as New England Biolabs with Cold Spring Harbor Laboratory, and Abbott Laboratories with Purdue University. A number of universities are also exploring the possible forming of industry/university cooperative research centers in some aspects of biotechnology. Finally, topics in the biotechnology area were included in the last small business innovation research solicitation. Over 100 proposals have been received from small businesses and are competing for phase I awards.

From our experience, several problems face universities, industry, and Government in the development of university/industry co-

operative research. One is the possible restriction of information exchange on progress in research when dealing with proprietary issues of industry. Another concerns the ownership of patents and the nature of licensing agreements. The Foundation is experimenting with and evaluating various modes of industry university interactions to better understand these concerns.

In the near term, our experience has been that issues such as academic freedom, publications and patents can be dealt with through open discussion between industry and the university and do not require Government action or intervention. There is a great deal of discussion and concern about these issues as relationships are being established, but they tend to diminish once the research begins. While the issues are important, the industry-university partners seem to be able to accommodate the interests of each in a way which contributes to the public good.

Further, my Division has an active program through the innovation processes research program to assess each of our operational programs. Thus, we will be able to suggest what kinds of relationships seem to work and why. This knowledge will then be made available to the funders of the research and to potential university and industry participants in these relationships.

It should be noted that the NSF is coordinating its biotechnology activities with other Government programs in the Office of Technology Assessment, the National Institute of Mental Health, and the National Institutes of Health.

In closing, I would like to give you my view of the benefits of cooperation between university and industry researchers. First, these programs leverage Federal funds for general research, training and instrumentation. Industry funding of university research now stands at less than 4 percent of the total funds, compared to nearly 70 percent for the Federal Government. Anything that can be done to increase industry participation, I feel, is in our best interests.

Second, programs such as industry/university cooperative research centers provide continuity of funding, strengthening academic departments, and enhance graduate student and postdoctoral training.

Third, cooperation improves job opportunities for graduates of the participating unversities, at the same time enhancing the transfer of knowledge embodied in these graduates to industry.

Last, but not least, cooperation does enhance information exchange between universities and industry and this information is made available to the larger scientific community.

Despite the potential for more catalytic encouragement from NSF and other Federal agencies, major initiatives for exploring the full range of possible cooperative activities must come from the academic and industrial sectors themselves. Though the objectives and roles of industry and universities in the national research and development system are different, they are, in many ways interdependent. Thus, the opportunity to identify and explore common ground in areas ranging from educational quality and skilled personnel shortages to scientific and engineering research instrumentation and multiresearch interests presents one of the major challenges of the 1980's. Such linkages must be approached only with careful attention to preserving the characteristics of the universi-

ties and of industries which have underpinned their success in their respective spheres of activity.

At this time, I would offer to provide you with any further information on this topic of university/industry cooperation, and would welcome your questions.

[The prepared statement of Dr. Senich follows:]

STATEMENT OF DR. DONALD SENICH, DIRECTOR, DIVISION OF INDUSTRIAL SCIENCE AND TECHNOLOGICAL INNOVATION, NATIONAL SCIENCE FOUNDATION

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE:

I AM PLEASED TO REPORT TO THE COMMITTEE THE NATIONAL SCIENCE FOUNDATION'S EXPERIENCE IN FOSTERING UNIVERSITY-INDUSTRY COOPERATION IN BIOTECHNOLOGY RESEARCH. I AM THE DIRECTOR OF THE DIVISION OF INDUSTRIAL SCIENCE AND TECHNOLOGY INNOVATION. DR. ROBERT RABIN, THE DEPUTY ASSISTANT DIRECTOR FOR THE DIRECTORATE FOR BIOLOGICAL, BEHAVIORAL AND SOCIAL SCIENCES IS WITH ME TODAY TO ASSIST IN ANSWERING YOUR QUESTIONS.

THE FOUNDATION AND THE NATIONAL SCIENCE BOARD ARE CURRENTLY EXAMINING THE ISSUE OF UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH. THE BOARD WILL ISSUE A REPORT TITLED, "UNIVERSITY-INDUSTRY RESEARCH RELATIONSHIPS: MYTHS, REALITIES, AND POTENTIALS" LATER THIS SUMMER.

I SHOULD NOTE AT THE VERY OUTSET THAT THE FOUNDATION CURRENTLY DOES NOT HAVE A LARGE NUMBER OF UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH PROJECTS OR PROGRAMS IN BIOTECHNOLOGY. WE DO HAVE EFFORTS TO INCREASE KNOWLEDGE IN AREAS OF BIOTECHNOLOGY AND TO ENCOURAGE UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH. THESE TWO EFFORTS ARE CONVERGING AND I CERTAINLY EXPECT MORE COOPERATIVE BIOTECHNOLOGY RESEARCH IN THE NEAR FUTURE. IN THE MEANTIME, THE FOUNDATION'S EXPERIENCE IN DEVELOPING A NUMBER OF PROGRAMS DESIGNED TO FACILITATE UNIVERSITY/INDUSTRY INTERACTION I BELIEVE IS APPROPRIATE TO THE TOPIC BEING ADDRESSED BY THIS COMMITTEE.

THE NATIONAL SCIENCE FOUNDATION ALSO HAS SEVERAL PROGRAMS OF SUPPORT FOR BASIC AND APPLIED RESEARCH IN BIOTECHNOLOGY WITHIN THE BIOLOGICAL, MARINE AND MATERIAL SCIENCES, AS WELL AS ENGINEERING. RESEARCH BASED UPON THE MODERN TECHNIQUES DEVELOPED IN THESE AREAS PROMISE MAJOR ADVANCES AND IMPROVED NEW PRODUCTS IN INDUSTRIES INCLUDING AGRICULTURE, FERMENTATION, WASTE DISPOSAL, MINING, PHARMACEUTICALS AND ENERGY PRODUCTION. AS EXAMPLES, THESE DEVELOPMENTS ARE EXPECTED TO REDUCE DEPENDENCE ON PETROLEUM, INCREASE THE NUTRITIVE VALUE AND STRESS RESISTANCE OF AGRICULTURAL CROPS, AND INCREASE EFFICIENCY IN THE USE OF RAW MATERIALS.

RENEWED INTEREST BY INDUSTRY IN SUPPORTING AND COLLABORATING WITH ACADEMIC SCIENTISTS RESULTS PRIMARILY FROM NEW TECHNOLOGY DEVELOPED IN THE BIOLOGICAL SCIENCES IN RESEARCH UNIVERSITIES. INDUSTRIAL SUPPORT OF ACADEMIA HAS BEEN SIGNIFICANT AND IS LIKELY TO INCREASE IN THE NEAR FUTURE.

THE FOUNDATION'S INDUSTRIAL SCIENCE AND TECHNOLOGICAL INNOVATION DIVISION IS EXPLORING AND EVALUATING SEVERAL STRATEGIES FOR INDUSTRY/UNIVERSITY COOPERATION. AT THIS POINT, I'D LIKE TO BRIEFLY DESCRIBE THREE PROGRAMS MOST INVOLVED IN THESE EFFORTS.

FIRST, IS THE INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH PROJECTS PROGRAM WHICH HAS BEEN OPERATING SINCE 1978. ITS OBJECTIVE IS TO STRENGTHEN COOPERATIVE SCIENCE AND ENGINEERING RESEARCH ON SPECIFIC PROBLEMS OR ISSUES OF MUTUAL INTEREST TO UNIVERSITY AND INDUSTRIAL SCIENTISTS.

RESEARCH PROPOSALS FOR THIS PROGRAM ARE PREPARED AND SUBMITTED JOINTLY BY ACADEMIC AND INDUSTRIAL INSTITUTIONS. TO ENSURE THE HIGH TECHNICAL QUALITY OF THE PROPOSED RESEARCH, THE ADMINISTRATION OF THE PROGRAM REQUIRES THAT THE PROPOSALS ARE SUBJECTED TO THE SAME HIGH STANDARDS OF PEER REVIEW AS THOSE ADDRESSED TO THE TRADITIONAL RESEARCH DIRECTORATES AT NSF. FURTHER, AS IN ALL NSF RESEARCH, THE RESULTS OF RESEARCH FROM THIS PROGRAM ARE INTENDED FOR PUBLICATION IN THE SCIENTIFIC AND ENGINEERING LITERATURE.

UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH PROGRAM PROPOSALS ARE SUBMITTED DIRECTLY TO THE NSF PROGRAM RESPONSIBLE FOR THE AREA OF RESEARCH. IF THE PROPOSAL IS SUCCESSFUL, THE GRANTS ARE JOINTLY SPONSORED AND FUNDED BY THE NSF PROGRAM IN THAT RESEARCH AREA AND THE UICRP PROGRAM. NSF ALWAYS PAYS FOR THE COSTS OF UNIVERSITY RESEARCH IN THESE PROJECTS. IN ABOUT ONE HALF OF THE PROJECTS, THE FIRM (OR FIRMS) COVERS THE COST OF ITS OWN PARTICIPATION. FOR THE REST, NSF PROVIDES SOME LIMITED FUNDS TO COVER INDUSTRY COSTS. IT IS CURRENT POLICY THAT NSF WILL PAY ONLY UP TO 50% OF THE COSTS OF THE INDUSTRIAL PARTICIPANT EXCEPT FOR SMALL BUSINESSES, WHICH MAY RECEIVE UP TO 90% OF THEIR COSTS. REQUIRING A FIRM TO PAY A SIGNIFICANT PORTION OF ITS RESEARCH COSTS ENSURES THAT THE PROPOSED RESEARCH IS CONSIDERED A PRIORITY ITEM BY THE FIRM'S MANAGEMENT. NSF FUNDS ARE NOT INTENDED TO SUBSTITUTE FOR FUNDS THE FIRM WOULD NORMALLY COMMIT FOR RESEARCH BUT DO PROVIDE FOR NEW AND EXPANDED COOPERATIVE RESEARCH PROGRAMS WITH UNIVERSITIES.

ON THE BASIS OF A RECENT EMPIRICAL ASSESSMENT OF THE PROGRAM CONDUCTED

99-177 O - 82 - 10

BY OUR INNOVATION PROCESSES RESEARCH SECTION (NSF, ASSESSMENT OF THE INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH PROGRAM, INTERIM REPORT #1, DESCRIPTIVE ANALYSIS OF PROJECTS FY 1978-1980), IT IS CLEAR THAT THE PROGRAM IS ATTRACTING HIGH-QUALITY RESEARCHERS FROM PRESTIGIOUS UNIVERSITIES AND TECHNOLOGY-ORIENTED COMPANIES. APPARENTLY, THE AMOUNT OF INTERACTION BETWEEN UNIVERSITY AND INDUSTRIAL SCIENTISTS IS SIGNIFICANTLY ENHANCED BY THE PROGRAM SINCE ABOUT TWO-THIRDS OF THE ACADEMIC PARTICIPANTS HAVE HAD ONLY LIMITED CONSULTANT OR EMPLOYMENT RELATIONSHIPS WITH THEIR FIRM PARTNERS. THIS REPORT IS AVAILABLE FOR YOUR INSPECTION.

THE SECOND PROGRAM IS THE UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH CENTERS PROGRAM INITIATED IN 1973. ITS PURPOSE IS TO INCREASE KNOWLEDGE IN TECHNOLOGICAL AREAS OF MUTUAL CONCERN TO UNIVERSITIES AND INDUSTRY. NSF PROVIDES SUPPORT FOR ONLY THE INITIAL DEVELOPMENT OF THESE CENTERS. IT IS EXPECTED THAT THE CENTERS WILL BE SELF SUPPORTING IN 3 TO 5 YEARS. NSF AND INDUSTRY'S SUPPORT IN INITIATING A CENTER PROVIDE FOR A BROAD-BASED RESEARCH PROGRAM, ONE LARGE ENOUGH TO BE OF INTEREST TO INDUSTRY BUT TOO LARGE FOR ANY ONE COMPANY TO UNDERTAKE ALONE. RESEARCH PROGRAMS OF THE CENTERS GENERALLY CORRESPOND TO THE UNIVERSITY'S AREAS OF EXCELLENCE. MOST CENTERS HAVE AN INTERDISCIPLINARY RESEARCH PROGRAM TO MEET INDUSTRY'S RESEARCH NEEDS. ALL CENTERS ARE EXPECTED TO INCREASE THE INDUSTRIAL SUPPORT FOR THEIR RESEARCH PROGRAM AS NSF SUPPORT IS PHASED OUT WITHIN A PERIOD OF 5 YEARS OR LESS. A CENTER IS CONSIDERED A SUCCESS WHEN ITS RESEARCH FUNDING IS AT LEAST AT ITS ORIGINAL LEVEL, BUT NO LONGER DEPENDENT ON NSF SUPPORT.

A CENTER IS INITIATED BY A PLANNING GRANT TO STUDY POSSIBLE ALTERNATIVES FOR STRUCTURE AND CONTENT OF THE RESEARCH PLAN AND TO EVALUATE INDUSTRY'S INTEREST IN A POTENTIAL CENTER. EACH CENTER DEVELOPS ITS OWN CHARACTER AS DETERMINED BY THE PRINCIPAL INVESTIGATOR, THE UNIVERSITY POLICIES AND OBJECTIVES, AND THE POTENTIAL FIRM SPONSORS. THE ADVICE AND EXPERIENCE OF NSF PROGRAM OFFICERS ARE ALWAYS AVAILABLE, BUT MANAGEMENT IN THIS AND SUBSEQUENT STAGES IS THE RESPONSIBILITY OF THE UNIVERSITY, WITH ADVICE FROM ITS INDUSTRY PARTNERS.

THIS PROGRAM, IN PART, PROVIDED THE RATIONALE FOR THE STEPHENSON-WYDLER TECHNOLOGY INNOVATION ACT OF 1980. THE CONTINUED GROWTH OF THE CENTER PROGRAM IS PART OF NSF'S RESPONSE TO MEETING THE REQUIREMENTS OF THE ACT.

I SHOULD NOTE THAT WE ARE ALSO ASSESSING THIS PROGRAM AS IS REQUIRED BY THE ACT. ONE OF THE PRODUCTS OF THAT ASSESSMENT WILL BE A PRACTICE MANUAL, OR "COOKBOOK," ON ESTABLISHING AND OPERATING A CENTER.

SIX INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH CENTERS ARE NOW IN OPERATION, WITH ONE ALREADY SELF SUFFICIENT. THESE CENTERS OPERATE WITH A TOTAL BUDGET OF APPROXIMATELY $4.3M THIS YEAR, OF WHICH INDUSTRY PROVIDES ABOUT $3.3M. IN FY 1982, WE EXPECT THE TOTAL BUDGETS FOR THESE CENTERS WILL APPROACH $6M WITH INDUSTRY PROVIDING ABOUT $4.5M. THE INDUSTRY/GOVERNMENT COFUNDING RATIO OF 3 TO 1 FOR THE CENTERS PROGRAM CLEARLY DENOTES THE CATALYTIC EFFECTS OF FEDERAL FUNDS.

THE LAST PROGRAM IS NSF'S SMALL BUSINESS INNOVATION RESEARCH PROGRAM

WHICH WAS STARTED IN 1977 TO ENCOURAGE QUALITY PROPOSALS FROM SMALL BUSINESSES TO NSF. I KNOW THAT YOU ARE AWARE OF THIS PROGRAM, SO I WILL BE BRIEF IN MY PRESENTATION.

THIS PROGRAM HAS THREE PHASES. IN PHASE I, PROPOSALS ARE INVITED FROM SMALL FIRMS IN 15 TO 25 SPECIFIC AREAS OF RESEARCH INTEREST TO NSF AND ARE PEER REVIEWED BY NORMAL NSF PROCEDURES. SUCCESSFUL PROPOSALS ARE SUPPORTED UP TO $30,000 FOR SIX MONTHS TO STUDY THE FEASIBILITY OF VARIOUS SCIENTIFIC OR ENGINEERING APPROACHES TO TECHNICAL PROBLEMS. AT THE END OF PHASE I, THOSE STUDIES CONSIDERED MOST LIKELY TO BENEFIT BY CONTINUING SUPPORT ARE ELIGIBLE FOR PHASE II AWARDS. PROPOSALS FOR PHASE II, WHOSE PURPOSE IS TO VERIFY THE SOUNDNESS OF THE RESEARCH APPROACH, ARE AGAIN SUBJECTED TO THE NORMAL COMPETITIVE PEER REVIEW PROCESS. PHASE II AWARDS HAVE AVERAGED $200,000 FOR UP TO 2 YEARS. PHASE III IS TO PURSUE COMMERCIAL APPLICATIONS, WHERE POSSIBLE, FROM THE PHASE I AND II RESULTS AND IS TO BE FUNDED ENTIRELY BY PRIVATE CAPITAL SOURCES.

THIS PROGRAM PROVIDES AN INCENTIVE FOR THE GRANTEE TO PURSUE COMMERCIAL APPLICATIONS BASED ON THE PROGRAM'S RESEARCH RESULTS. PROPOSERS ARE ENCOURAGED TO DEVELOP COOPERATIVE ARRANGEMENTS WITH UNIVERSITY RESOURCES. MOST GRANTEES HAVE USED UNIVERSITY RESEARCHERS AS CONSULTANTS OR SUBCONTRACTORS FOR SPECIALIZED ACTIVITIES.

WE ARE ALSO IN THE PROCESS OF ASSESSING THIS PROGRAM. OUR ASSESSMENT IS NOT COMPLETE BUT I CAN TELL YOU THAT SOME SMALL BUSINESSES SUPPORTED UNDER THIS PROGRAM HAVE OBTAINED PRIVATE CAPITAL FOR THE DEVELOPMENT OF

NEW PRODUCTS AND PROCESSES. ONE HAS ALREADY REACHED THE MARKETPLACE. NEW FIRMS HAVE BEEN STARTED AND AT LEAST 15 INVENTIONS HAVE BEEN REPORTED.

ALL THREE PROGRAMS HAVE BECOME INVOLVED IN BIOTECHNOLOGY. THE INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH PROJECTS PROGRAM HAS FUNDED A NUMBER OF PROJECTS LINKING TOGETHER FIRMS AND UNIVERSITIES SUCH AS UPJOHN WITH BAYLOR UNIVERSITY, NEW ENGLAND BIOLABS WITH COLD SPRING HARBOR LABORATORY, ABBOTT LABORATORIES WITH PURDUE UNIVERSITY, MAPLEHURST FARMS, AND WILSON FOODS ALSO WITH PURDUE, ARCHER DANIELS MIDLAND COMPANY WITH MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND CELANESE WITH YALE UNIVERSITY. A NUMBER OF UNIVERSITIES ARE ALSO EXPLORING THE POSSIBLE FORMING INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH CENTERS IN SOME ASPECTS OF BIOTECHNOLOGY. ONE FORMAL PROPOSAL HAS BEEN RECEIVED AND IS BEING REVIEWED. FINALLY, TOPICS IN THE BIOTECHNOLOGY AREA WERE INCLUDED IN THE LAST SMALL BUSINESS INNOVATION RESEARCH SOLICITATION. OVER 100 PROPOSALS HAVE BEEN RECEIVED FROM SMALL BUSINESSES AND ARE COMPETING FOR PHASE I AWARDS.

FROM OUR EXPERIENCE, SEVERAL PROBLEMS FACE UNIVERSITIES, INDUSTRY, AND GOVERNMENT IN THE DEVELOPMENT OF UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH. ONE IS THE POSSIBLE RESTRICTION OF INFORMATION EXCHANGE ON PROGRESS IN RESEARCH WHEN DEALING WITH PROPRIETARY ISSUES OF INDUSTRY. ANOTHER CONCERNS THE OWNERSHIP OF PATENTS AND THE NATURE OF LICENSING AGREEMENTS. CONSEQUENTLY, THE FOUNDATION IS EXPERIMENTING WITH AND EVALUATING VARIOUS MODES OF INDUSTRY UNIVERSITY INTERACTIONS TO BETTER UNDERSTAND THESE CONCERNS.

IN THE NEAR TERM, OUR EXPERIENCE HAS BEEN THAT ISSUES SUCH AS ACADEMIC FREEDOM, PUBLICATIONS AND PATENTS CAN BE DEALT WITH THROUGH OPEN DISCUSSION BETWEEN INDUSTRY AND THE UNIVERSITY AND DO NOT REQUIRE GOVERNMENT ACTION OR INTERVENTION. THERE IS A GREAT DEAL OF DISCUSSION AND CONCERN ABOUT THESE ISSUES AS RELATIONSHIPS ARE BEING ESTABLISHED, BUT THEY TEND TO DIMINISH ONCE THE RESEARCH BEGINS. PROBLEMS THAT HAVE ARISEN TO DATE ARE MORE EASILY DEALT WITH THAN EITHER PARTY ANTICIPATED.

FINALLY, IT IS NSF'S INTENTION TO PROVIDE SEED MONEY AND ADVICE TO HELP GET THESE PROGRAMS STARTED AND PROVIDE SOME GENERAL MODELS FOR OTHERS TO FOLLOW. WE ARE ASSESSING THE ARRAY OF POSSIBLE UNIVERSITY/INDUSTRY RELATIONSHIPS TO SEE WHICH SEEM TO WORK IN WHAT SITUATIONS AND IN WHAT TECHNOLOGICAL AREAS. NSF HAS SUPPORTED A WIDE RANGE OF PROJECTS: INDIVIDUAL RESEARCHERS STARTING A SMALL BUSINESS (WITH THE SBIR PROGRAM); UNIVERSITY-BASED CENTERS HAVING MORE THAN 30 COMPANY SPONSORS (UICRC); AND MULTIPLE UNIVERSITY, MULTIPLE COMPANY RESEARCH PROJECTS. IN DOING SO WE HAVE LEARNED HOW TO AVOID CERTAIN ISSUES AND ARE PASSING THIS EXPERIENCE ON TO INTERESTED INSTITUTIONS OR PARTIES.

FURTHER, INDUSTRIAL SCIENCE AND TECHNOLOGICAL INNOVATION HAS AN ACTIVE PROGRAM THROUGH THE INNOVATION PROCESSES RESEARCH SECTION TO ASSESS EACH OF OUR OPERATIONAL PROGRAMS, SMALL BUSINESS INNOVATION RESEARCH, UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH, AND UNIVERSITY/INDUSTRY COOPERATIVE RESEARCH CENTERS. THUS, WE WILL BE ABLE TO SUGGEST WHAT KINDS OF RELATIONSHIPS SEEM TO WORK AND WHY. THIS KNOWLEDGE WILL THEN BE MADE AVAILABLE TO THE FUNDERS OF RESEARCH (INCLUDING NSF) AND TO

POTENTIAL UNIVERSITY AND INDUSTRY PARTICIPANTS IN THESE RELATIONSHIPS.

IT SHOULD BE NOTED THAT THE NSF IS COORDINATING ITS BIOTECHNOLOGY ACTIVITIES WITH OTHER GOVERNMENT PROGRAMS IN THE OFFICE OF TECHNOLOGY ASSESSMENT, THE NATIONAL INSTITUTE OF MENTAL HEALTH, AND THE NATIONAL INSTITUTE OF HEALTH. WORKSHOPS HAVE BEEN COFUNDED WITH NIH AND NIMH. INFORMATION HAS BEEN PROVIDED FOR AN OTA STUDY IDENTIFYING GROWTH AREAS IN BIOTECHNOLOGY. NSF REPRESENTATIVES HAVE MADE PRESENTATIONS ON UNIVERSITY/INDUSTRY COOPERATIVE EFFORTS TO NIH ADVISORY COMMITTEES.

IN CLOSING, I WOULD LIKE TO GIVE YOU MY VIEW OF THE BENEFITS OF COOPERATION BETWEEN UNIVERSITY AND INDUSTRY RESEARCHERS. FIRST, THESE PROGRAMS LEVERAGE FEDERAL FUNDS. INDUSTRY FUNDING OF UNIVERSITY RESEARCH NOW STANDS AT LESS THAN 4% OF THE TOTAL FUNDS, COMPARED TO NEARLY 70% FOR THE FEDERAL GOVERNMENT. ANYTHING THAT CAN BE DONE TO INCREASE INDUSTRY PARTICIPATION IN BASIC AND APPLIED RESEARCH, I FEEL IS IN OUR BEST INTERESTS. SECOND, PROGRAMS SUCH AS INDUSTRY/UNIVERSITY COOPERATIVE RESEARCH CENTERS PROVIDE CONTINUITY OF FUNDING, STRENGTHENING ACADEMIC DEPARTMENTS, AND ENHANCING GRADUATE STUDENT AND POST-DOCTORAL TRAINING. THIRD, COOPERATION ENSURES JOB OPPORTUNITIES FOR GRADUATES OF THE PARTICIPATING UNIVERSITIES, AT THE SAME TIME ENHANCING THE TRANSFER OF KNOWLEDGE EMBODIED IN THESE GRADUATES TO INDUSTRY. LAST, BUT NOT LEAST, COOPERATION DOES ENHANCE INFORMATION EXCHANGE BETWEEN UNIVERSITIES AND INDUSTRY. THIS INFORMATION IS MADE AVAILABLE TO THE LARGER SCIENTIFIC COMMUNITY THROUGH PRESENTATIONS, PUBLICATIONS OR INFORMAL CONVERSATIONS.

AT THIS TIME, I WOULD OFFER TO PROVIDE YOU WITH ANY FURTHER INFORMATION ON THIS TOPIC OF UNIVERSITY/INDUSTRY COOPERATION, AND WOULD WELCOME YOUR QUESTIONS.

Mr. WALGREN. Thank you very much. I have some ground I would like to go over with both of you.

Coming at this whole area without a great deal of specific understanding and knowledge, what concerns me is that the Federal Government will be providing resources which are then taken advantage of by other private sector entities, with the total benefit flowing to the private sector. My own preference with the changes in the patent laws, essentially is to just simply allow more private, wholly private, interest in what develops out of that mixed research. Moreover, it seems to me it is not in the least certain that the Federal Government's interest, or the public's interest, will ultimately be protected properly.

I wonder whether we are asking the right questions. For example, Dr. Senich, in your summary you indicated that industry is providing only 4 percent of total university research funds, and the Federal Government is providing 70 percent. That may indicate, if the situtation is such that private industry retains substantial rights to benefit from any results of the research, that they are simply leveraging their benefit. The more money the Government puts in, the more leveraged benefit the private sector takes out. It doesn't seem obvious to me, at least on its face, that the Federal interest is really protected. So I wonder what your reaction to that is.

Dr. SENICH. May I address that first?

Mr. WALGREN. Sure.

Dr. SENICH. Let me just go from the 4 percent to the 70 percent, by citing an example.

I was reading last year's testimony during which Dr. Gray, president of MIT, discussed the programs at Massachusetts Institute of Technology, in particular the polymer center. I alluded to the fact that that center is now operating at about $700,000 a year, totally with private funds. NSF provided about $500,000 starting in 1973 to seed the start of that center. It is now totally self-sufficient. I brought along a piece of material called SLA, super lightweight ablator. This material was not developed with NSF funds. But instead, it was developed with private industry funds at the Massachusetts Institute of Technology. This material is now being used by NASA to cover the external shell of the recoverable shuttle tanks. It is esimated by the manufacturing company, in this case Martin Marietta, that on every shuttle flight, by using the improved method and this material, NASA will save $100,000.

It is estimated that during the decade of the 1980's, we will be able to save upward of $40 million on the recoverable shuttle tank costs. I don't know whether that, is a public good coming out of research. But in my opinion, it is. And this is a demonstration of what we are getting out of our center's program.

While we have not patented anything out of the centers right now, it seems reasonable to me that all members of the consortium of companies that belong to a center, share equally in that center's output.

The patents belong to the university. At each of the centers, for example, the center at Ohio State or the center at Rensselaer Polytechnic Institute, each of the members participates in a nonexclusive royalty-free license arrangement. I am not an economist, but I

believe that if something were to be developed and placed in the marketplace, that the public does benefit from it.

Support for the centers comes not only from the Government and from the industry, but there is also the contribution from the universities putting their own money into this activity through facilities, salaries, and other support. So the three parties, the Government, industry, and the university are all sharing in the cost and all ultimately share in the public good.

Mr. WALGREN. I think that that argument certainly is sound, at least insofar as the centers are concerned. But I still have the reservation that when we are funding university research as opposed to the centers, we now are taking Federal moneys and trying to cause something to happen between the private sector and universities. Hopefully there will be products such as you mentioned and we hope they are developed in that center, and we are willing to let the public's interest be protected by the fact that that center wouldn't exist if the public funds weren't put there.

But when we, as a Congress, fund university research, or fund an in-house-based research contract, as I believe this Massachusetts General Hospital-Hoechst arrangement to be, we don't really have this same expectation for private profit. In fact, our research budgets for universities would be much greater than we put into the centers, I would imagine.

I am not sure about that, but I know that the motive behind putting the dollar there is different. I guess what I am wondering is, in the university area, as opposed to the centers, are we comfortable with the protections for the public dollar?

Dr. SENICH. In the case of our university/industry cooperative research projects program, where we fund the total portions of the university and only a portion of industry costs, what we are funding, is basic research. This basic research is no different than research which would be done in the Materials Research Division, or the Physiology, Molecular and Cellular Biology Division of NSF. The products coming out of the research are open publications. It is the same kind of research that would normally be accomplished in the discipline divisions.

In my opinion, we have leveraged a great deal more because we are probably adding some relevance to the research by adding a new dimension. Also, sometimes we are able to capture the use of instruments which otherwise wouldn't be available to us.

So I do think that, in the long run, the public benefits by providing support to the industry/university cooperative research projects.

Mr. WALGREN. Well, I certainly agree that the public does benefit. Moreover, the public would benefit even if the private sector were to make and then deliver the product whole cloth, the public would benefit.

My reservation is that NSF budget is relatively limited. Particularly these programmatic budgets are very limited when you consider the overall NSF budget. I can see taking those dollars, limited dollars, and putting them into the centers and not worrying about the interest of the public in the dollar. However, when you get into the broader research expenditures, and particularly the range of Government assistance to universities, and then we find that

money leveraged out by the university to the private sector, I know that we are not really contemplating that when the Congress places the public dollar in their hands and it seems that we ought to be at least somewhat concerned about that.

Mr. WALGREN. Dr. Raub, the NIH has sent their team to Massachusetts General Hospital, is that right?

Dr. RAUB. Yes.

Mr. WALGREN. You are satisfied that people understand the rights and liabilities. But can you describe the level of our satisfaction? What report did they bring back that makes us feel comfortable?

Dr. RAUB. I can, sir. I led that team, and so have some firsthand recollections of our degree of satisfaction, which is not unmitigated but is a strong feeling that every reasonable arrangement has been made, and every likely and not so likely problem has been indentified, and there was preparation to deal with them.

Mr. WALGREN. Perhaps there are several questions from Mr. Gore that might be worth raising at this point. Then feel free to generally respond to that opening of mine.

You made the site visit at Massachusetts General Hospital. What were the reasons for approving the conditions of the contract, if they could be itemized?

Dr. RAUB. The primary reason is that the MGH and Hoechst, had gone to considerable pains in drafting the contract to insure that all of the applicable Federal laws and regulations were applied. To the extent any Federal money would be involved directly in any of the inventions developed under that work, there was no question but that the Federal laws would apply.

And, therefore, other terms of that contract that might have given Hoechst an exclusive license would not be valid. That is, MGH as holder of the invention and ultimate patent would be following the intent of Public Law 96-517 in the award of licenses rather than specific terms of the Hoechst-MGH agreement.

As a way of preventing difficulties, specific arrangements had been made to insure as far as possible that the primary, if not exclusive, funding of that new department would be from non-Federal sources—that is, would be directly from Hoechst. A number of other administrative procedures were put into place to identify even the possibility of commingling of funds well in advance of development of any invention.

It was really that set of principles and demonstrated good understanding of their responsibilities that made us come away comfortable with the arrangements that MGH had effected.

Mr. WALGREN. It is my understanding that OMB has a set of guidelines that concern commingling of funds under 96-517.

Dr. RAUB. That is correct.

Mr. WALGREN. Are you satisfied that the Massachusetts General Hospital-Hoechst agreement is consistent with those guidelines in addition to whatever interpretation of the law as might be?

Dr. RAUB. Yes, we are.

Mr. WALGREN. If I understand this correctly, OMB decided not to have a de minimis provision in its guidelines for governing 96-517.

Dr. RAUB. That is correct.

Mr. WALGREN. Does that mean that any Federal funds that were used in a certain sector of the activity would qualify that area as being infused with Federal funds; is that correct?

Dr. RAUB. That is our interpretation, and I believe that is OMB's interpretation. The language of the statute, if I can quote from memory, says Federal funding "in whole or in part" and does not establish any minimum level for what that funding might be.

In developing its guidance, while OMB decided not to have the de minimis provision, it did include a few examples to distinguish direct funding from indirect funding. And it suggested that the latter would not establish a Federal interest in the invention. For example, if Federal funds had been used to construct the building, and sufficient time had passed for the residual Federal interest to lapse, then the fact of that construction with Federal funds would not establish a Federal interest in research done in that building solely on private money. Whereas, if instrumentation, not only purchased with, let's say, NIH funds, but continuing to be operated with funds from NIH, were made available at less than the full cost of their service to an industrially funded activity, that would constitute direct funding. Further, that would bring that entire activity under the provisions of Public Law 96-517 and therefore establish in part the Federal interest in the activity, making the invention-reporting, licensing requirements and other disclosure requirements applicable in that case, notwithstanding any other contractual agreement between that university and any particular industrial organization.

Mr. WALGREN. Were there representatives of the Hoechst Corp. involved in your discussions?

Dr. RAUB. No, sir.

Mr. WALGREN. Do you know whether there was any change in what might have been originally contemplated under the agreement in light of your representation of the Federal interest?

Dr. RAUB. I don't believe that our visit per se triggered any changes. My understanding and my recollections from the discussion was that, during the drafting of the agreement itself, there was considerable change from the original attitudes and orientation of both parties as they strove to strike some compromise in their respective interests that finally was manifest in that agreement.

To the best of my knowledge, the event of an NIH site visit did not produce any material change, nor did we suggest that it produce any change in that contract.

Mr. WALGREN. In your visit did you review the total agreement as it exists between Massachusetts General Hospital and Hoechst?

Dr. RAUB. Yes, sir.

Mr. WALGREN. Was there anything in that agreement that you felt was inconsistent with the present interpretation of Federal policy?

Dr. RAUB. No, sir.

Mr. WALGREN. So it is your testimony that that agreement is consistent with present interests that we are trying to protect?

Dr. RAUB. Yes, sir.

Mr. WALGREN. And present interpretation of the law that protects that interest?

Dr. RAUB. Yes, sir.

Mr. WALGREN. Let me ask you if you would generally discuss with me the experience with this for-profit sector involvement with NIH grants, and whether the possibility of conflict of interest with private sector interests has arisen at all in the area of grants to for-profit organizations.

Dr. RAUB. There is virtually zero contemporary experience with NIH grants to for-profit organizations. The policy change to which I alluded in my testimony occurred this past January. We are only now beginning to get the first wave of grant applications from for-profit organizations.

We identify in prospect the possibility of some concerns, for the interests of the public and the NIH in particular are different from the interests of private corporations. Under the patent and trademark amendments, small businesses, as you will recall, are eligible to the same rights that not-for-profit organizations are now. So we expect perhaps different kinds of relationships between us and small businesses than with large businesses.

We expect to be quite careful and very thorough in our review of those grant applications to insure that there is full disclosure of the research activity and its implications both for our program missions and the interests of those organizations.

We enter this optimistic that both we and they will be able to manage whatever problems arise and that the larger good from the participation of this segment of the R&D community in our programs will far outweigh whatever administrative difficulties we may have in keeping these problems either nonexistent, or otherwise under control.

Mr. WALGREN. So what you are saying is that it is so new that we don't have any experience with it?

Dr. RAUB. Yes, sir.

Mr. WALGREN. But you are sensitive to it?

Dr. RAUB. Yes.

Mr. WALGREN. And you are looking for it. I gather that there has been an effort to include private sector scientists on peer review panels. Has there been any indication that possible conflicts of interest from these private sector scientists will affect their participation in those efforts?

Dr. RAUB. There has been an effect, as manifest in a reluctance—or, in some cases, a refusal—of for-profit scientists to accept an appointment on a review group for fear that there might be restraints on their full participation in that peer review. These are not restraints imposed by us, but rather restraints arising from their own corporate responsibilities.

It has not been a significant problem to date. The groups with which we have worked have been quite candid in raising their concerns. We have had for many years a small percentage of our peer reviewers as scientists from for-profit organizations.

And the current effort is oriented toward raising that number to give us a broader representation. I don't expect that the problems or the restraints will be such that they will prevent our having an improved representation in those committees.

But there is no doubt that many of those scientists see themselves under different restraints than those that would apply to the average university scientists.

Mr. WALGREN. You had indicated in your statement, Dr. Raub, that there is new guidance to NIH grantees and contractors on patent rights, I believe.

Dr. RAUB. Yes, sir, I did.

Mr. WALGREN. You are now drafting such guidance. Is there anything that might be said as to the general principles that you are following and what the status of that effort is, and whether all contractors will have a formal patent policy that corresponds to those guides?

Dr. RAUB. To answer the questions in reverse order, we are not likely to require any particular patent policy, but will be strongly urging our awardees to have a patent policy and will be prepared to provide some assistance as to what alternative policies might be considered.

Mr. WALGREN. Does that include universities?

Dr. RAUB. Yes, sir, universities and other recipients of our awards. The time line is such that we hope to have the document available this summer or early in the fall. Pending the necessary clearances within the executive branch, we hope to be able to issue it some time this fall.

The intent in the document is to provide a simple and workable distillate of the law and OMB guidelines in a form that all of our awardees can make ready use of, especially those who have little or no experience in the pursuit of inventions, the handling of invention rights, the seeking of patents and the commercialization of those patents.

If I may expand for just another minute or two on this, the current patent law is similar in many ways to a set of administrative practices that the NIH had evolved over the past decade or so. Under the former law, NIH had evolved the practice called institutional patent agreements, [IPA's] whereby institutions could enter into agreements with NIH that would have given them first rights to the inventions that they developed under NIH funding.

Those first rights and their subsequent obligations related to the seeking of patents and the granting of licenses and the reporting on their activities served as a model for the current legislation. Before that legislation went into effect, there were approximately 80 institutions that had those institutional patent agreements negotiated with us.

So functionally they are in almost an identical situation under the new laws as they were under those special agreements. By contrast, the hundreds of other institutions had been relating with us on an invention-by-invention basis, without any overarching agreement. And for the first time most of them are confronting the idea of having an internal set of policies and practices.

It is that latter group in particular to which we are aiming our guidance. We believe we can further the public interest by promoting commercialization from those organizations, as well as from the 80 that already have well established internal systems.

Mr. WALGREN. At the outset, did you say that this policy would apply to all grantees?

Dr. RAUB. Yes, sir—all except large businesses.

Mr. WALGREN. Let me ask one other question, going back to the commingling problem. How specifically do you advise your grantees on accounting in order to prevent any commingling?

Dr. RAUB. Part of this guidance will deal with the issues of comingling of funds. The OMB circular speaks to this issue, making the point that separate accounting of Government funds and commercial funds are perhaps a necessary, but not sufficient condition to insure the separation of the interests.

We expect to build on that and elaborate it as necessary for the guidance of our awardees.

Mr. WALGREN. I apologize for having overextended. I am going to have to go now or I will miss that vote. I think we really have come to the useful end of what I have to ask both of you.

Thank you very much.

With that, we will close the hearing.

[Whereupon, at 3:45 p.m., the subcommittees adjourned.]

APPENDIX

WASHINGTON UNIVERSITY

SCHOOL OF MEDICINE
660 SOUTH EUCLID AVENUE
ST. LOUIS, MISSOURI 63110
(314) 454-3242

Busch Professor and Chairman
DEPARTMENT OF MEDICINE

Physician-in-Chief
BARNES HOSPITAL

June 30, 1982

Honorable Albert Gore, Jr., Chairman
Subcommittee on Investigations and Oversight
Committee on Science and Technology
House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

We enjoyed the opportunity to appear before the two subcommittees on June 16 to discuss the Washington University-Monsanto research agreement. We have heard reports of testimony on the second day of the hearing (June 17) which related to our agreement and felt it might be worthwhile to expand upon certain areas in order to present as complete a picture as possible. We hope, Mr. Chairman, that you can make this letter a part of the hearing record.

We are in agreement with the five general principles which Robert Rosenzweig, Stanford's Vice President for Public Affairs, argued should "guide the formulation of policy" with respect to industry-university research relationships.

Perhaps the application of Rosenzweig's "fourth principle," namely, "the choice of scientific questions to investigate must reside with the faculty who will do the research", has not been clearly understood in the case of the Washington University-Monsanto agreement.

The agreement underwrites research in a broad area of science. Information about this area is circulated to investigators in a request for particular proposals. Investigators will respond with appropriate specific research plans which fall into the broad area under consideration. The committee of eight (four from Washington University and four from Monsanto) will accept (or reject) projects from these proposals. No proposal will be funded which is not set forth by members of the faculty. Investigators are free to submit proposals unfunded under the agreement to any other source of support, public or private.

The evenly divided committee of eight was proposed during the long gestation of this agreement by a member of the Washington University faculty. It is deemed to represent the partnership notion of this agreement and the spirit of consensus without which the agreement cannot endure.

The committee cannot originate research proposals nor can it prevent research proposals from seeking other funding.

The fact that the agreement supports research in a broad area of science hardly differs from the practice of most funding agencies. Broadly defined research areas are funded with the knowledge that many investigators are involved in those areas from whom a significant response would come. Research interests at Washington University School of Medicine are compatible with the basic concerns of the agreement. This is the attraction of the agreement.

Questions were also raised on June 17 about restrictions upon free discussion by scientists. We believe this matter has been adequately elaborated upon in the letter to you of June 18 from Edward MacCordy, Associate Vice Chancellor for Research at Washington University.

It is important in examining our agreement to understand that the partners have worked with each other for years, and have come to respect and know each other. There may be some difficulties from time to time in this "marriage," but the agreement was made, and its execution will be carried out, in the full spirit of the kinds of principles which Robert Rosenzweig described to the subcommittees.

Mr. Chairman, the Saint Louis Post Dispatch, in its June 17th edition, headlined its story of our appearance before your subcommittee as "Monsanto Defends..." the agreement with Washington University. We certainly did not feel at all defensive about the agreement. Rather, we felt that our appearance took place in an atmosphere of interest, inquiry, and support and not in one of an adversary tone. We feel we all have much more to learn about new approaches to support of basic research. We are excited about our agreement and its positive implications, and appreciate the assistance of the subcommittees.

Please call on us if you have additional questions or comments.

Sincerely,

David M. Kipnis

Dr. David Kipnis

Howard A. Schneiderman

Dr. Howard Schneiderman

WASHINGTON UNIVERSITY

ST. LOUIS, MISSOURI 63130

OFFICE OF THE ASSOCIATE VICE CHANCELLOR FOR RESEARCH

JUN 22 1982

June 18, 1982

EDWARD L. MACCORDY

ASSOCIATE VICE CHANCELLOR
FOR RESEARCH

TELEPHONE
(314) 889-5889

Honorable Albert Gore, Jr., Chairman
Investigations and Oversight Subcommittee
House of Representatives
Congress of the United States
Washington, DC 20515

Dear Mr. Chairman:

In testimony before your Subcommittee on Wednesday, June 16, 1982, concerning the research agreement between Washington University and Monsanto, you asked a question about clause 9.3 of our agreement which addresses the matter of verbal presentations and discussions by university investigators. My response in the hearing was not as informative as it might have been and I would like to take this opportunity to provide a more complete explanation.

During negotiation of the research agreement, it was recognized that the standard of divulgation of European patent law does not allow any public disclosure of an invention, orally or in print, before the filing of a patent application under threat of instant loss of all European patent rights. Strict observance by the university of this standard could restrict the normal academic communications of our investigators, a situation neither the University nor Monsanto finds acceptable.

Consequently, the parties have addressed the problem through efforts to anticipate the making of inventions, to detect them as early in the research process as possible, and thereupon to promptly file patent applications. Preferably, this will be done before the inventing investigator feels a need to discuss his invention publicly in seminars, conferences, etc. Of course in many cases the first divulgation will be through the scientific publication process and this too is to be carefully monitored for inventions. This set of preventive activities is summarized in clause 9.4 of the agreement and further dealt with in clauses 5.6, 6.1, 6.3, 9.1, 9.2, 10.2, 11.2, 11.3, 11.4 and 11.5.

Thus, the intent of clause 9.3 is to have the Monsanto legal staff provide specialized legal advice to the University for use in educating our investigators as to the potential effect of their personal activities on the future establishment of European patent rights protecting their inventions. This is a rather technical matter with which neither our administration nor faculty is well acquainted. With a better understanding of this matter, we are confident that faculty members will voluntarily and effectively deal with the problem without any degradation in scientific communications with their students, scientific colleagues and the public.

99-177 O - 82 - 11

A prime objective of this research agreement is to bring resulting new technology to the public worldwide through the established channels of trade and commerce. In addressing this objective, our desire is to support the United States' international trade position by providing to the sponsoring U.S. firm, the Monsanto Company, proprietary rights for its advantage in foreign markets.

Finally, I would point out that the European divulgation problem for university investigators is not unique to industrial research agreements, but is an equally important issue in the preservation of foreign patent rights derived from government-sponsored research. Considerable attention was paid to this issue by the Office of Management and Budget and the sponsoring government agencies in preparing the implementing regulations, OMB Circular A-124, for Section 6 of Public Law 96-517.

Thank you for this opportunity to comment further on the question raised in your Subcommittee hearings.

Sincerely,

E. L. MacCordy

cc. Dr. Howard Schneiderman
Dr. David Kipnis
Mr. Robert Blackburn

ELM/jva

STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

OFFICE OF THE PRESIDENT

July 16, 1982

Representative Albert Gore, Jr.
Chairman, Subcommittee on Oversight
and Investigations
House Committee on Science and Technology
1131 Longworth House Office Building
Washington, D.C. 20515

Dear Representative Gore:

Your Subcommittee, in May of this year, held hearings on the Commercialization of Research in Biotechnology. At those hearings, testimony was presented by Albert H. Meyerhoff on behalf of the Natural Resources Defense Council. I hope the record is still open, because Mr. Meyerhoff's testimony contains at least one error so striking that it requires correction.

In connection with a discussion of the efforts of universities to deal internally with conflicts of interest, Mr. Meyerhoff states "An attempt, last year, for example, at Stanford to adopt a modest conflict of interest proposal was voted down resoundingly by its faculty." Exactly the opposite is true. No conflict of interest policy was defeated, resoundingly or otherwise. On the contrary, a new policy was brought to our Academic Senate by the Committee on Research; that policy requires the disclosure, on request from the Dean, the Provost, or the President, information regarding the nature of consulting agreements, the companies involved, and the number of days committed per consulting agreement. That proposal was passed by the Senate on October 15, 1981.

I hope very much that the record of the hearing can include the above paragraph as a correction.

With thanks and best regards.

Sincerely yours,

Donald Kennedy
President

cc: Albert Meyerhoff

Natural Resources Defense Council, Inc.

25 KEARNY STREET
SAN FRANCISCO, CALIFORNIA 94108
415 421-6561

SEP 17 1982

Washington Office
1725 I STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006
202 223-8210

New York Office
122 EAST 42ND STREET
NEW YORK, N.Y. 10168
212 949-0049

September 13, 1982

Congressman Albert Gore
Committee on House Science and
Technology
Investigations and Oversight
Subcommittee
819 House Annex No. 1
Washington, D.C. 20515

Dear Congressman Gore:

In his letter of June 16, 1982, Donald Kennedy has raised an issue concerning Stanford's conflicts of interest code, discussed in my testimony to the Subcommittee. We appear to be discussing two different codes. The proposed code I referred to was one recommended by the Stanford Committee on Research. While modest, it would have prevented Stanford University from entering into research contracts with firms in which faculty members had an equity interest. A copy of that proposed policy is enclosed. It was never adopted by the Stanford faculty. (Indeed, Stanford has recently entered into an agreement with a firm known as "Engenics" in which several Stanford faculty members have a financial interest.) My understanding that this policy was actually formally rejected by the Stanford faculty was based upon a conversation with a spokesman from Stanford's public relations department. This was incorrect, and I apologize for the misimpression. In fact, apparently through a parliamentary maneuver, the provision was dropped from the eventual code acted on by the faculty. (See attached minutes of the Academic Council, at 8.) However, how this proposed policy actually met its fate is not particularly important.

What is important is whether Stanford has acted to require public disclosure of financial interests held by its faculty potentially benefitting from research projects funded in whole or in part with public funds. This was the context of my remarks to the Committee. Neither Stanford nor any other major research university has adopted a conflict of interest code requiring such disclosure. The code referred to by Dr. Kennedy in his letter, a copy of which is enclosed, is to put it charitably, cosmetic. It fails to require any public disclosure whatsoever. It requires minimal disclosure, and then

100% Recycled Paper

only upon request, within the University. No disclosure, even internally is required of the amount of income received by Stanford University scientists from their outside relationships with private corporations or other business entities. A cover letter from Stanford Associate Dean Patricia DeVaney to me concerning the intent of their code makes this point clearly. She states:

> President Kennedy has asked me to respond to your December 11 letter to him regarding Stanford policy on conflict of interest and financial disclosure by faculty. Enclosed is a copy of the University's policy statement on outside consulting activities of the faculty. As you will see, the policy has been recently revised (revisions noted in italics) to reflect recent changes as approved by the Senate of the Academic Council, the faculty body which represents all faculty members on matters of academic policy.
>
> I should note, however, that neither the Senate's recent discussions nor the policy statement enclosed has dealt with the issue of financial disclosure of faculty. It has always been University policy to not require information from the faculty regarding the amount of money they receive from their non-University related activities. They are really required (and only then upon specific request from the University) to disclose the number of days spent consulting and the general nature of such agreements.in cases where questions of conflicts of interest have arisen.

Letter to Albert Meyerhoff from Patricia L. DeVaney, Associate Dean of Graduate Studies and Research, December 22, 1981, copy enclosed.

Stanford received at least $120,000,000 in federal research funds in FY 1980. The Stanford policy does next to nothing in assuring the public that these funds are being used for the public interest and not for the personal gain of the Stanford faculty. In that connection, a copy of a recent California magazine article on university-industry collaboration dealing with Stanford and other California universities is enclosed. I request it be made part of the record.

The need for federal intervention is heightened, not reduced, by an examination of Stanford's purported conflict of interest policy.

Sincerely,

Albert H. Meyerhoff
Attorney-at-Law

encls.
cc: President Donald Kennedy

STANFORD UNIVERSITY
STANFORD, CALIFORNIA 94305

OFFICE OF THE VICE PROVOST
AND DEAN OF GRADUATE STUDIES AND RESEARCH

December 22, 1981

Mr. Albert M. Meyerhoff
Regional Counsel
California Rural Legal Assistance
2111 Mission Street, Suite 401
San Francisco, California 94110

Dear Mr. Meyerhoff:

President Kennedy has asked me to respond to your December 11th letter to him regarding Stanford policy on conflict of interest and financial disclosure by faculty. Enclosed is a copy of the University's policy Statement on Outside Consulting Activities of the faculty. As you will see, the policy has been recently revised (revisions noted in italics) to reflect recent changes as approved by the Senate of the Academic Council, the faculty body which represents all faculty members on matters of academic policy.

I should note, however, that neither the Senate's recent discussions nor the policy statement enclosed have dealt with the issue of financial disclosure of faculty. It has always been University policy to not require information from the faculty regarding the amount of money they receive from their non-University-related activities. They are merely required (and only then upon specific request from the University) to disclose the number of days spent consulting and the general nature of such agreements in cases where questions of conflict of interest have arisen.

If you have further questions, please feel free to call me at (415) 497-3763.

Sincerely,

Patricia L. Devaney
Associate Dean of Graduate
Studies and Research

enclosure

E MEMORANDUM • STANFORD UNIVERSITY • OFFICE MEMORANDUM • STANFORD UNIVERSITY • OFFICE MEMORANDUM • STANFORD UNIVERSITY • OFFICE

As the next item of business, Chairman Abernethy called up the Annual Report for the Academic Year 1980-81 submitted by the Committee on Research (SenD#2311). ANNUAL REPORT OF C-Res

Professor I. Olkin, in summarizing the Annual Report, said that the work of the Committee had been focused on a limited number of questions. C-Res had been asked to review the conditions under which proprietary research is carried on at the Stanford Synchrotron Radiation Laboratory (SSRL). C-Res concluded that those conditions are in conformity with our standing policies regarding secrecy in research and saw no reason to recommend change in the conditions. C-Res had also been asked to review a proposal which three companies offered to fund the construction of three new beam lines at SSRL in return for guaranteed access to the beam lines for a renewable period of three to five years. C-Res had endorsed the proposal subject to the condition that no proprietary research be conducted within the sponsors' guaranteed beam access time.

A substantial part of the work of C-Res had been devoted to consideration of the effect of potential commercialization of University research results, on which C-Res was now prepared to make some recommendations (see below)

Professor B. Roth asked whether any new federal regulations bearing on research have been promulgated. Dean Lieberman said that the International Traffic in Arms Regulations (ITAR) are being revised, and any changes in those regulations may well affect us. That is a complex issue and nothing has as yet been settled.

In reply to a question from Professor C. C. Lougee, Professor Olkin said that C-Res had been asked to comment on proposals for changes in the indirect cost recovery rate. The Committee did so and advised Dean Lieberman.

In reply to a question from Professor R. E. Taylor, who inquired about secrecy restraints; (who, he asked, decides on the question of restraints: is it C-Res or the Stanford administration?); Dean Lieberman said that Stanford would not enter into agreements which placed restraints that do not comply with our policies.

Professor W. C. Reynolds asked about the response of outside commercial sponsors to an indirect cost recovery rate of 73%, as compared with the much lower internal rate. Dean Lieberman said that the only objection had come from the EPRI (Electric Power Research Institute) organization.

On the motion to accept the Annual Report of C-Res (SenD#2311) (subject to the Committee's withdrawal of the final clause of the third full paragraph on page 2) the Senate, by an undivided voice vote, accepted the report.

Chairman Abernethy then directed attention to a set of policy proposals submitted by C-Res (SenD#2319) to deal with cases in which "the potential intellectual propercy resulting from the (University-based) research offer significant and unprecedented opportunities for commercialization." POLICY PROPOSALS ON DEVELOPMENT OF SPONSORED RESEARCH

There was much discussion of the first proposal submitted by C-Res, dealing with disclosure, upon request from the cognizant Dean, the Provost,

or the President of the names of companies for whom faculty members perform consulting services, the general nature of the consulting services, and the number of days committed per consulting agreement.

Professor Olkin said that our current policy limits consulting work to 13 days per quarter. This policy is not actively enforced, nor are faculty members asked to disclose the names of their clients.

Acting in that same spirit of non-policing of faculty consulting activities, C-Res was not asking for routine policing, on the grounds that only in the exceptional case is the (possible) invasion of faculty privacy justifiable.

Professor K. L. Melmon said that he had substantial disagreement with the proposal. These were difficult issues but they seemed not to have been fully thought out.

Why, he asked, should the reporting of a potential conflict of interest be dependent on the decision of an individual researcher? A faculty member who does not foresee a potential conflict might enter into a consulting agreement, only to discover afterwards that a real conflict exists. If we had regular reporting by all faculty members on consulting activities, other people might be able to foresee potential conflict of interest. Further, he said, the proposal specifies only certain administrative officers at the level of Dean or higher, whereas in the School of Medicine Chairmen of Departments are required to guarantee that no departmental faculty are in risk of conflict of interest. We need to rethink the question of reporting on consulting activities so that those persons who are guarantors of the absence of conflict of interest can do so responsibly and informedly.

Professor Olkin said that any School can impose restrictions that are more stringent than the University-wide policy that was being proposed. It would be difficult, and undesirable, to make the reporting in detail of consulting activities a routine procedure.

Dean Lieberman said that the issue of conflict of interest is a difficult one. However, faculty are subject to a policy, listed in the Administrative Guide (Guide Memo 15.2) which deals with conflict of interest and situations requiring disclosure. That policy dates back to September 26, 1966. There is a faculty responsibility to be sensitive to possible conflict of interest for which no administrative regulation can adequately substitute.

Professor V. A. Harvey said that it is in principle good that faculty members should be expected to act on the prodding of their consciences on matters of ethics and morals, but in the modern world the disentangling of ethical matters may prove to be a very difficult task. As a way of dealing with that dilemma, why should not faculty members be asked to report routinely on their consulting activities? Professor Olkin replied that C-Res judged the routine reporting of consulting activities to be a potential invasion of privacy.

Professor B. Roth said that we seem to have two different kinds of policy statements. One relates to the 13 days per quarter on which faculty are permitted to perform consulting work external to Stanford: another purports to deal with consulting as it relates to work carried out inside Stanford. We need clear guidelines on what constitutes or might constitute conflict of interest. In a future that may well involve increasing dependence on industrial support for University

research, we shall need clarification, not individual opinions on conflict of interest. Could C-Res not provide some examples of situations in which a conflict might arise?

President Kennedy said that the policy proposed by C-Res represented only a first step towards requiring disclosure. But we should move slowly in the matter of requiring more disclosure information: Large amounts of faculty and administrative time might be consumed.

Professor R. H. Maffly asked: under what conditions does a requirement for disclosure arise? On knowledge received by the Dean's Office? On the basis of newspaper reports? On reports from departmental faculty members?

Professor B. A. Babcock, who said that Professor Maffly's question on the origin of a cause to request disclosure was a valid one, proposed to modify the policy statement by removing the first phrase of the policy. That amendment was seconded by Professor Harvey, but was defeated on a divided voice vote.

Professor J. H. Merryman said that it had been stated that this policy statement is a first step. Yet we shall need a much more carefully drafted statement; and C-Res should perhaps this year focus attention on that need. Reference had been made to the "Heffner" statement on conflict of interest in 1966: that statement related to much simpler circumstances than those of today. It is unrealistic to say that regulations are unworkable or, alternatively, that we must rely on the sensitivity of faculty members. We need material which will lead to better appreciation of potential conflict. What are typically recurring problems or situations? Can we describe hypothetical situations which would constitute a guide?

After some further discussion the policy recommendation (as recorded in the attachment to these Minutes) was adopted on a divided voice vote.

Chairman Abernethy then called attention to a second policy recommendation, dealing with the distribution of royalty income derived from research results arising in Stanford-based research. Several members sought, without success, to obtain clarification of the language of the recommendation. Was it intended that, as soon as the cumulative income from a given licensing arrangement had amounted to one half of a department's operating budget <u>over a period</u> of years, the department would thereafter receive no further royalty income? Or was it intended that as soon as the royalty income from a given licensing arrangement amounted <u>in a given year</u> to one half of the department's operating budget, no further income would accrue to the department <u>during that year</u>?

Professor K. V. Melmon said that Schools have a considerable interest in the development of patents, but that different Schools have different formulas for budgets. Why should the policy be based on departmental operating budgets? Why not on School budgets?

Professor K. J. Arrow said that our principal interest as a University resides in the scholarly work of the faculty. We do not, or should not, need "incentives" either for Schools or departments to engage in research with the aim of making "big hits."

Professor S. M. Dornbusch, seconded by Professor W. C. Reynolds, moved to refer the proposal back to C-Res on the grounds that it was so unclearly drafted

that the Senate could not discern its true intent. The motion carried on an undivided voice vote.

President Kennedy raised a question regarding the propriety of the Senate's adopting a resolution that would bear so heavily on what are basically administrative matters. The Secretary gave it as his opinion that the distribution of royalty income is essentially a budgetary matter over which the Senate has no authority. Any proposal adopted by the Senate could only have the force of advice to the administration and could not properly be held to constitute academic policy.

Chairman Abernethy drew attention to a third item in SenD#2319 - one relating to equity participation by Stanford in outside companies that might be involved in the commercial development of Stanford-based research results. Chairman Abernethy said that this was not an item requiring any Senate action.

Professor S. M. Dornbusch said that the tone of Recommendation III might be improved, particularly in Sections A,2 and B. Professor K. L. Melmon said that words such as "significant stockholder" are vague and unhelpful.

Professor K. J. Arrow said that terms such as "significant interest" enter into documents such as SEC regulations and people successfully work with such terms. He added that although he believed that the general idea of proscribing University participation in company activities, he agreed with Professor Dornbusch that there was a contradiction in the language of sections A,2 and B.

President Kennedy said that although Recommendation III might not be appropriate for Senate action, nevertheless it would be very useful to have expressions of Senate members' views on whether Stanford should have a permissive or a proscriptive policy on equity participation.

FROM THE MINUTES OF THE FOURTEENTH SENATE OF THE ACADEMIC COUNCIL, November 12, 1981

DISCUSSION OF EQUITY PARTICIPATION

At approximately 4:40 p.m., Chairman Abernethy introduced as the last item of business a discussion of Equity Participation, i.e., participation by the University in the commercial development of Stanford-based research results. Chairman Abernethy noted that in a recent report to the Senate the Committee on Research had submitted, without a request for action by the Senate, a recommendation that the University should participate in such ventures to only a limited degree and under defined conditions (SenD#2319).

At the invitation of Chairman Abernethy, Professor I. Olkin said that both the faculty and the administration recognize the need to explore new methods of funding. Equity participation does provide the potential for new funding, and the main question that arises is: what will equity participation do to the fabric of the University? Problems are bound to arise, and the issue is whether, on balance, the potential problems outweigh the gains or not. On this point the members of C-Res were not of one mind.

Professor Olkin drew attention to an article written by Art Buchwald which, he said, contained some exaggerations but nevertheless bore on the problem. Professor Olkin cited from the report of C-Res the following list of potential problems:

(i) perceived or real conflicts of interest in such areas as faculty appointments and promotions, space allocations, salary levels, etc., for faculty involved in joint ventures with Stanford;

(ii) unintended encouragement of (a) secrecy in research or (b) distortion of graduate student training in areas of research that may be potentially financially rewarding but no longer advance the frontiers of basic science;

(iii) conflicts in selecting which faculty members' research results deserve University investment for proposed commercialization;

(iv) difficulty in avoiding the appearance of conflict vis-a-vis the public benefit; e.g., the University could be subject to accusations of unfair profit from its research.

Professor Olkin observed that industrial corporations sometimes have short-term needs that override long-term goals. There have, moreover, been previous cases (e.g., the Harvard-Monsanto Corporation agreement of the 1970s) which were compromised by violating the principle of open communication. Indeed, in the case referred to there was no faculty involvement in the selection of the investigator who would benefit from Monsanto's guarantee of ten years of support: that is, there was no peer review.

Members of C-Res felt, on balance, that the problems of equity participation might prove to be too great a risk to encourage Stanford to become involved.

Professor J. B. Keller noted that universities need money from private sources, especially when public sources are diminishing. The best opportunity for becoming involved in participation arises at the formation of a new business because a gift received or an investment made then yield a large return. Clearly the profit-making prospects of a new venture must be assessed before investing, but the most likely opportunities for getting in at the start are to be found in faculty-related ventures. Naturally, the disadvantages must be weighed against the advantages. It seems unreasonable to expect to be able to do this weighing in general, without knowing the specific details.

Professor Keller added that some of the dangers are present regardless of whether the University is a participant or not. A faculty member, for instance, can withhold research results from a colleague whether or not the University has a share in a business. And diversion of the direction of graduate students is a hazard that is always present. If University participation were to take place, the influence on professors would probably vary from case to case.

Benefits to the University might be outright gifts of shares or returns on investment - though it should be recognized that new ventures sometimes fail. The possibility that we might become involved in a new corporation as, say, Hewlett-Packard can only exist if we continue to make important discoveries. Few cases involving a large investment are likely to arise, and we could weigh the advantages and disadvantages on a case-by-case basis.

Professor J. H. Merryman said that he was glad that he was not called on to make a decision. It is difficult to decide on the basis of hypothetical scenarios. As a lawyer he was interested in observing how decisions are made. The Senate, he said, cannot usefully discuss issues of this kind in the abstract: we need to have concrete cases to look at.

Professor J. L. Adams asked whether C-Res had prepared any hypothetical scenarios. Professor Keller said that in a real case in the School of Medicine one professor was not discussing research results with another professor because the latter was involved in a different venture. Professor Merryman reemphasized that the question is too abstract for productive and rational discussion: concrete examples are needed.

President Kennedy offered to talk about two quite different concrete situations.

First, in the case at Harvard, there was a dramatic instance of how things can go wrong. Harvard was asked to participate with a faculty member whose research was being carried on down the hall from another professor who had a major interest in a Swiss company working in the same scientific field.

Second, in the case of Hewlett-Packard, he wished Stanford had a nickel for every dollar that Hewlett-Packard had made. But, when that company was formed the two scientists involved did not retain a connection with the University. Stanford could have become an investor but did not do so.

President Kennedy said he wished to provide a contrast between a situation in which one of the participants continued to maintain a university connection and the other, in which the inventors left the university and set up a separate organization.

Professor R. E. Taylor said that President Kennedy had written some eloquent remarks, with which he agreed, on the subject of participation. He asked whether President Kennedy felt that his hands are tied by our present policy.

Professor J. L. Adams asked whether Professor Merryman believed that we do not need a policy to deal with the abstract situation. Professor Merryman replied that the essential principles are well known: the problem is to apply those principles to a particular case.

Professor V. R. Fuchs asked whether at Harvard the problem had arisen because one professor was already involved in a commercial venture. President Kennedy said that Harvard would probably say that a conflict of interest might not have arisen had the second professor not had a financial interest in the Swiss company. Professor Fuchs asked what would happen if the University were to become involved with a professor's discovery and then, later, another professor became involved in similar work. President Kennedy replied that at Harvard the situation heightened that kind of problem.

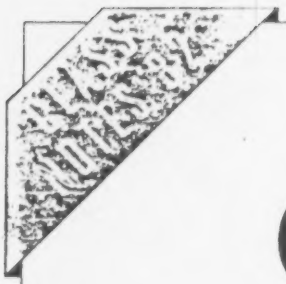
In answer to a question from Chairman Abernethy, President Kennedy agreed that even if no other professor were involved it is always possible that the allocation of resources to a co-participant professor could be viewed as the action of a university holding a vested interest in that professor's work.

Professor Fuchs said that such a situation escalates what already exists in the case of professors who have large grants and contracts that contribute to overhead. President Kennedy said that the two cases are not similar. Indirect cost recovery is in no sense a profit: by law we can only recover (and, at that, incompletely) for actual costs generated by research work.

Professor K. J. Arrow said that some members of the Senate were having some difficulty in looking at the problem. Suppose, he said, that a professor were to make a discovery with commercial possibilities and asked the University to provide some financing. In such a situation there is no clear arm-length relation between the professor and the University (as a potential investor). Such an investment, if made, would be a diversion of our endowment. How can the University protect itself against unwise ventures or imprudent investments, particularly if the request comes from a distinguished member of the faculty? President Kennedy said that a nice point had been raised. How, he asked, once an institution starts to participate in ventures with Professor A, can it turn around and tell Professor B that all its venture capital is tied up in A?

Professor B. Roth said he agreed with President Kennedy's written statements on this subject. Stanford is not in the venture capital business: Stanford is not in business at all, in that sense. We need funds, but we should be distorting our role if we were to go out and sell anything except a first-class education. The conflict of interest is certainly one, but only one aspect. There are certain things that it is legitimate for a university to do and others that are not, regardless of who initiates the venture.

Chairman Abernethy said that the discussion had been somewhat inconclusive. The hypothetical examples had not been carefully stated. At a later time we may have concrete examples to consider. He thanked all the participants for their contributions. Meeting was adjourned



THE GENE MERCHANTS

Biology—it's a wonderful field. Why, it's like cloning money! If you're smart, you, too, can become a millionaire. Just be sure to keep a lock on your experiments.

IN APRIL 1977, HOMER COLE LAY DYING IN A LOS ANGELES HOSPITAL of acute myelogenous leukemia. Although he knew his condition was beyond hope, in the name of scientific research he agreed to undergo a painful medical procedure, the sampling by suction of his cancerous bone marrow. Two months later he died.

Not so, however, his extracted blood-making cells. They attained a kind of immortality when two UCLA Medical School hematologists, Phillip Koeffler and David Golde, fooled them into growing and dividing in a test tube. The scientists celebrated this achievement, as is the custom in the field, by christening the rare cell line after themselves: KG-1.

The new strain proved to be star-crossed. After a haphazard transcontinental odyssey, a sample eventually ended up back in California, in the hands of the gene-splicing wizards at Genentech, a South San Francisco company specializing in the brave new world of for-profit recombinant DNA research. Genentech's labs used KG-1 to successfully clone a bacterium that could produce a scarce and valuable protein called interferon as easily as cows give milk. Interferon is the body's natural defense against

BY WILLIAM BOLY

viral attack and, not so long ago, *Time* magazine's cover candidate for the Holy Grail of modern pharmacology—the cure for cancer. At the time, a patent on the means of producing it was thought to be very hot property, to the tune of a potential $3 billion in sales annually.

And so the improbable legal issue arose: who owned the commercial right to Homer Cole's interferon gene? Next spring, after more than two years of procedural wrangling, lawyers for the University of California, Genentech, and Hoffmann-La Roche, the multinational drug giant whose labs received the cell line from the National Cancer Institute (NCI) and first enhanced its interferon-producing capability, go to trial in San Francisco's federal court to settle the question. What won't be settled, however, is the graver issue—the incipient corruption of pure science in the era of the golden biolab.

In the case at hand, David Golde has allegedly (he denies it) described the KG-1 cell line as "stolen" and "hijacked" and Roche employees as "crooks" and "thieves." Roche, in turn, has amended its original complaint to include damages for libel and

STRAINED RELATIONS

A UC Davis biologist battles his students.

GENETIC ENGINEERING may have fattened the bank accounts of top professors in the field, but for graduate and postdoctoral students—the foot soldiers of basic research—the wave of spectacular profits has raised serious questions. Last year, student grumbles about a UC Davis molecular biologist, Professor Raymond Valentine, reached all the way to Congress.

Professor Valentine: His business affairs sparked a rebellion.

For the last several years Valentine's lab has been studying one of the more fabulous promises of genetic engineering, the idea that the nitrogen-fixing capability of a plant like the soybean could be transferred to cereal grains. The objective: self-fertilizing corn, rice, wheat—miracle hybrids that would be worth billions of dollars in savings to farmers.

By 1981, however, federal money was running out, so Valentine went prospecting for support and struck gold. Allied Chemical, one of the nation's leading fertilizer producers, agreed last summer to contribute $2.5 million to his research at Davis. A few days later, Allied further disclosed it was purchasing a 20 percent interest in Valentine's recently formed off-campus private research lab, Calgene, for an additional $2.1 million.

The conflict was obvious. Valentine, as officer and stockholder in Calgene, would be money ahead by ensuring that any patentable discoveries were channeled through his off-campus business. Acceding to pressure from Charles Hess, dean of environmental sciences, Valentine eventually withdrew from the Allied grant.

The story might have ended there except for a series of bombshell revelations about treatment of graduate students that were leaked to the press this spring. According to a memorandum from JaRue Manning, chair of the UC Davis bacteriology department, four of Valentine's five graduate students had elected to transfer out of his lab because Valentine had told them it was their responsibility to clear their research projects with Calgene. In other words, as one postdoc put it, "Calgene gets first crack at all our ideas." *Nature* reported that one of these students had been ordered, as a condition of further funding, to switch his thesis topic after spending two and a half years on it, and mentioned the fact that Valentine had not returned calls asking for an explanation.

This summer, however, Valentine was only too happy to discuss the flap, which he dismissed as based on misquotations: "I told the students that there was no research going on at Calgene that duplicated their research in my laboratory, and if they did not accept my word for it, they should go to Calgene and verify my statement."

The students are standing by their story, however, and have added some vivid details. Last September, says one, "the whole lab was fired twice en masse by Valentine. It was only Bill Rains, then director of the Plant Growth Lab, who kept it from sticking." Rains wouldn't comment. Valentine explains he merely "invited those more interested in conducting a crusade than science" to leave the lab.

Why get rid of the students? If overlap in research objectives between the university and Calgene constituted a conflict, says a former student, "one solution was to eliminate the source of competition. That's why he wanted us out." Another route was by assimilation. When Calgene hired away postdoc Shel Anderson, he took with him strains he had been working on in the university's lab. "Permission was granted," says Valentine, who also did the granting, as it turns out. Dean Hess later requested that the strains be returned, which they were.

But two former Valentine postdocs have another complaint. "Virtually all his time was spent setting up plans for Calgene," says one. As a result, says another, the caliber of the lab's science suffered. "Ray's been scooped twice in the past year," he says.

One of the traditional measures of a scientist's standing is how successful he is at obtaining funding. Valentine points out that the National Science Foundation (NSF) awarded him an extraordinarily large grant of $4 million in 1977 to pursue his study of the nitrogen-fixation gene. It is also true that the grant wasn't renewed. The emerging consensus, as *Science* recently summarized it, seems to be that self-fertilizing cereals will not happen soon, if at all. Not one gene but a whole complex is involved, and the amount of energy required to carry out the necessary metabolic processes looks prohibitive. Valentine attributes the nonrenewal to a change in the NSF's funding policy.

This summer, Dean Hess appeared before a House subcommittee in Washington to explain the problems at Davis. He testified that a research prof with business interests in the same field usually posed an unacceptable conflict to the university. Still, he hadn't accepted Valentine's offer to resign from the experiment station. Why not? "It's a gray area," Hess answers. "Ray has backed away from Calgene quite a bit. He was an officer, now he's only a consultant."

To be sure, the distinction between Valentine and the company is blurred by the fact that Calgene's greenhouse is located on his home acreage near Davis. Still, with a new crew of students in place, he expects a better year ahead. "The lab is humming along. We have a good, cohesive group of people. Our only problem is funding," he concludes, "like it normally always would be." —W.B.

The greatest danger to man posed by the recombinant technique was wholly unanticipated—the escape of the "venality gene" on campus.

slander. Robert Gallo, a senior NCI investigator who also felt his honor had been besmirched in the affair, at one point apparently offered to punch out Golde. A small misunderstanding. Golde thinks Gallo unwittingly gave away the store. Gallo thinks passing around cell lines to serious investigators is the way ethical scientists are supposed to behave.

Whatever its outcome, the bitter interferon dispute mirrors a widening schism at major research universities in California and, indeed, nationwide, between scientists who do and scientists who don't capitalize on their research. Biology has suddenly become big business. A novel life form, the professor-entrepreneur, has replicated on campus and threatens to take over whole departments of microbiology and immunology. This new species, cultured at great expense over the last 25 years by massive public subsidies, is surprisingly adept at attracting venture capital and stock options. Many whom we fondly thought of as absent-minded have become millionaires.

UC San Francisco's Herbert Boyer, whose borrowed $500 investment in Genentech turned into a paper $60 million on the opening day of the company's trading on the New York Stock Exchange, is only the most outlandish example. Dr. Ivor Royston of UC San Diego, who helped found Hybritech, has stock valued at $5 million. Applied Biosystems of Foster City advertises in science magazines that its just introduced gas-phase protein sequencer, a supersensitive device for ferreting out the chemical structure of hormones, is "based on research at a major California university." To be precise, it was developed in the lab of Caltech's Leroy Hood, who heads the Division of Biology there. Each one costs "100 K," according to a company spokesman, "and we've got sixteen heading out the door beginning in August." In all, about 200 firms hoping to capitalize on some aspect of the new biology have started up in the last few years, 25 in the Bay Area alone. Virtually all have a direct link to university expertise, either through consulting arrangements or equity holdings. "Almost all the leading people in the field have some industry connection," observes UC Santa Cruz chancellor Robert Sinsheimer.

Not that administrators object—the universities are too busy driving their own bargains to do much sermonizing. Industrialist Edwin Whitehead is giving $127 million to create an institute in his name at MIT, and in return the institute will have an unprecedented say in the appointment of faculty members. In California, Syntex Corporation, the Palo Alto–based merchandiser of birth control pills and sundry beauty aids, is entitled to eight days of work a year for five years from several dozen members of Stanford's Department of Medicine in exchange for a "substantial" but unspecified gift. The chemical engineering departments at Cal Berkeley and Stanford recently accepted a four-year, $7.5 million grant (channeled through a new, partly faculty-owned company called Engenics) from six major corporations. But the UC San Francisco med school lost the biggest catch of all when Professor Howard Goodman, one of the early DNA research pioneers, left the school in favor of Massachusetts General Hospital, taking a $70 million, ten-year funding commitment with him. The source: the giant West German chemical company Hoechst AG.

TO UNDERSTAND WHAT BROUGHT THE SUDDEN FLUSH OF business suitors, it helps to appreciate the staggering potential of recombinant DNA technology. DNA, deoxyribonucleic acid, the famed double helix whose design was unraveled by James Watson and Francis Crick in 1953, has long been understood to harbor the secret of life—how we renew ourselves from day to day and generation to generation. In its Morse code–like spiral of complementary base pairs, DNA carries the chemical instructions for making an arm, a wing, a fin, a tree limb—everything that lives. A gene is the basic functional unit on a strand of DNA. The average gene is about 1,500 base pairs long, and there are millions of genes arranged along the giant strands of DNA (which we call chromosomes) in each human cell. To visualize one cell's complement of DNA, picture 46 pieces of string (corresponding to the 46 chromosomes characteristic of the human species) laid end to end. The string would stretch all the way from San Diego to the Oregon border, with a new gene appearing along it every two feet. The proportions are about right. Yet the double helix is so cunningly fashioned, looped and turned back on itself, that the chromosomes occupy less than a pinpoint of space, each pinpoint a complete set of blueprints on how we are made.

Incredible as it seems, molecular biologists discovered in the mid-1970s how to cut genes out of the convoluted DNA chains at precisely controlled spots and splice in new ones. They do so by means of nature's own scissors and paste—restriction enzymes, ligases and endonucleases, and a complicated biochemical protocol. A recombinant DNA experiment resembles a chapter out of a Fanny Farmer cookbook—simmer, spin, heat, drain, let stand. Biochemists can tell what bacterial strain is culturing in the nutrient broth by smell—rotten peaches, wet dog, old running shoes. The development of the recombinant DNA technique has been compared to everything from the Darwinian revolution to the harnessing of the atom. Actually, it is more closely analogous to the invention of the microscope. Using the technique, scientists can peer deeper than ever into the molecular basis of life. "This is probably the most exciting time in the history of biology," says UC San Francisco biochemist Joe Hedgpeth.

It is also probably the most lucrative. Self-replicating *E. coli* bacterial "factories," their DNA altered to suit man's purposes, are already at work manufacturing insulin, interferon, human growth hormone, and a vaccine against hoof-and-mouth disease. But the commercial horizon for gene-splicing is vastly greater than the drug market. Students of organic chemistry have long recited a tongue-in-cheek ode: "Lord, I fall upon my knees/And pray that all my syntheses/May no longer prove inferior/To those run by bacteria." The natural fact alluded to by this doggerel is that biological production is perfectly capable of doing many of the jobs now performed by the synthetic chemical industry—making amino acid food supplements, solvents, plastics, fertilizers—with less energy expended and fewer pollutants emitted. Cetus Corporation of Berkeley has

(continued on page 170)

Contributing editor William Bole's last feature was "Travels in Humboldt" in the February issue.

99-177 O - 82 - 12

GENEMERCHANTS

(continued from page 79)

developed a process that would turn starch into fructose, a natural sweetener and an ingredient in such dietary staples as Coca-Cola. Cetus estimates the sugar-and-sweetener market at $11 billion a year. Summing up the possibilities, the Office of Technology Assessment has estimated sales for recombinant DNA products in the chemical and pharmaceutical industries alone at $15 billion a year by the turn of the century. All of which has led to a distinctly bull market for biologists.

To be sure, even scientists balked at the threshold of the genetic age. Speculation about Frankenstein-like creations coming out of the lab—a cancer or botulin as contagious as the Asian flu or microbes so well adapted to eating oil that they would wipe out world reserves—caused them to call a self-imposed moratorium on recombinant experiments. In 1975, at Asilomar, near Monterey, 140 leaders in the field gathered to establish guidelines. In retrospect, the great safety debate is viewed as something of a fool's errand. Nature is pretty efficient at filling ecological niches. The chances of a superlethal bug coming out of the lab have been likened to the chances of improving a Swiss watch by cramming a random piece of hardware inside the case. On the other hand, as a scientist wryly suggested in a recent issue of *Nature*, the single greatest danger to mankind from the recombinant DNA technique was wholly unanticipated at Asilomar—namely, the escape of the "venality gene" on campus.

THE MAN WHO BEST PERSONIFIES the conflicts of the researcher-turned-businessman is Herbert Boyer, cofounder of Genentech and professor of molecular biology at UC San Francisco. Fondly described by one of his biggest fans, *The Wall Street Journal*, as "a baroque angel in blue jeans," the plump, curly-haired Boyer, along with Stanford's Stanley Cohen, secured the patent to the basic recombinant technique. The two ceded their royalty interests in the patent to their respective universities—a selfless $1.5 million gesture somewhat diminished by questions over whether the patent is legally defensible.

Members of Boyer's lab during the mid-seventies, when Genentech was getting off the ground, describe him as an organizational genius capable of inspiring high excitement in his crew of postdoctoral understudies. "Herb would get so jazzed on an apparently trivial result, he'd get people going harder and harder and harder," says one. "It was one of those times when everything seemed possible."

But problems arose. "I remember that first day," another postdoc recalls. "There were only twelve or so of us in Boyer's lab, and one guy was singled out to have a confidential meeting with Herb and Bob Swanson [Genentech financial overseer and cofounder]. We all wondered what was going on, and he came back out and couldn't tell us. Right then, that very moment, things changed in the lab, and it sort of all fell apart from that point."

Rumors. Strained relationships. Says one former postdoc, who now runs his own lab, "You knew they weren't free to talk about their work. They were your friends, so you didn't want to make them feel awkward. So you sort of censored yourself." What was going on, of course, was the operation of two labs in one, the university's and Genentech's, with information dispensed on a "need to know" basis.

Particularly in the early years of its existence, the alliance benefited Genentech's image among investors as the bioengineering group that always seemed to get there first with the most, successfully altering bacteria to produce the brain hormone somatostatin in 1977, insulin in 1978, human growth hormone in 1979, interferon in 1980. Boyer also proved he could handle the press masterfully. The somatostatin announcement was front page stuff, in no small measure because of Boyer's vivid description of what it portended. The experiment showed that bacterial manufacture of insulin was practical. The cost would be "tens or hundreds of times lower" than chemical synthesis or isolation from animal glands. "The man in the street can now finally get a return on his investment in science," he told journalists.

Eventually, science writers began to suspect they were being used. When Genentech first announced the cloning of insulin, Judy Ismach of *Medical World News* wrote a dissent. "They hadn't proved the gene was biologically active," she says. "They hadn't published in a refereed journal. It was just a big media hype. It was done because Genentech was going public and they wanted the coverage."

Whatever the rationale, the business strategy worked. The Genentech offering made history on Wall Street as investors, eager to get a piece of the future, drove the price from $35 to $89 a share in the first hour and a half of trading. Herb Boyer, raised in rural Pennsylvania in a household without a car, was suddenly, surprisingly, a multimillionaire. As a child, his mother had advised him to get some education, learn how to type. There would always be jobs for typists. Boyer's reaction after his big score was to buy a Porsche Targa—not over budget, considering the circumstances.

Among Boyer's colleagues, though, necks stiffened at such wheeling and dealing. Dr. Paul Berg of Stanford, who convened the Asilomar Conference and was soon to receive the Nobel prize in chemistry (his cattier associates referred to it as the "Nobel prize for integrity"), reacted to the somatostatin announcement by praising the science and icing the scientist. Such commercial involvement, he said, "is just not to my taste. This isn't to criticize Herb particularly, but I just can't see it." Berg's stan-

dards were so lofty, it was reported, that he even avoided consulting work with pharmaceutical firms that could use his advice.

Opinions such as Berg's help explain how biologists got their reputation as the Trappist monks of science. Although it is easy to forget now, as little as ten years ago the nagging criticism of their research effort, preoccupied as it was with the functioning of *E. coli*, was that they had almost nothing to show for the billions of dollars the American people had poured into it. Until very recently, the people drawn to microbiology had little reason to expect to become wealthy. In fact, they were seduced by their own curiosity, by the intellectual challenge of solving the puzzle of how life works chemically. What mattered was the excitement of the hunt, the tiny, incremental bits of progress evident only to peers. And being first—not first to the bank, but first in line for the Nobel prize. In his account of solving the chemical structure of DNA, James Watson describes his reaction at Oxford after reading then Caltech professor Linus Pauling's clearly incorrect solution: "The moment the Eagle's doors opened for the evening, we were there to drink a toast to the Pauling failure. Instead of sherry, I let Francis [Crick] buy me a whiskey."

ON CAMPUS, THE RECOMBINANT DNA revolution has arrived. Where Herb Boyer once endured the snubs of his colleagues, there are now four separate bioengineering businesses connected to members of his department, including one affiliated with the former biochemistry and biophysics chairman, Bill Rutter. As for Paul Berg, in 1980 he helped recruit the blue-ribbon board of scientific advisers for the nascent DNAX Research Institute of Molecular and Cellular Biology, physically located in Palo Alto but incorporated on the Isle of Jersey in the English Channel. This spring, a little more than a year after DNAX's formation, the organization announced that it had been acquired by the Schering-Plough Corporation (Coppertone, St. Joseph's Aspirin, Maybelline cosmetics) for $29 million. Under the terms of the deal, Paul Berg and the rest of the science board had their speculative shares in DNAX converted into hard-money Schering-Plough stock. What makes an infant business with no products worth $29 million? Answered a Schering-Plough spokesman, "The company's assets are far and away the working scientists and scientific advisory board." Berg explained his updated outlook on commercial involvement this way: "After all these years of doing the research and insisting how important it is to mankind, it is somewhat hypocritical to be negative when the possibilities to apply this information are presented."

Not quite everyone has seen the light, however. Leon Wofsy, a Berkeley professor of immunology who has turned down "quite a few knocks at the door," saw fit to raise his voice against the "reigning silence" on campus last spring. Wofsy, never one to hold his tongue, was last in the public eye during the National Guard occupation at Berkeley in 1969. Governor Reagan had called a group of concerned profs on the carpet to administer a public tongue-lashing, television crews invited. Wofsy responded in the middle of the dressing-down, inciting a debate that so flustered Reagan that he left the room, cameras grinding footage that was seen that evening coast to coast. It was one of the few media confrontations Ronald Reagan has ever lost.

Now, however, Wofsy's cause is the integrity of academe. In a widely publicized open lecture at Berkeley last March citing chapter and verse, he staked out his position in favor of the technology, against the "rising entrepreneurial tide" on campus. As one vivid example, he described the competition for the services of a junior faculty member at Stanford. Two biotechnology companies were in the bidding, each touted by a different senior faculty member. When the young man made his choice, the losing senior prof told Wofsy, "Well, you know what that means. He won't be able to use my equipment. We're business competitors now." As Wofsy sees it, the conflict between running a biotechnology business and doing publicly funded biotechnology research is straightforward. "The business of business is to make money, to beat the competition, and the mode is secrecy," whereas "the motive force of the university is the pursuit of knowledge, and the mode is the open exchange of ideas and unrestricted publication of the results of research." One man can't follow both imperatives, he implies.

Reaction from colleagues was less than enthusiastic. "I got the West Point treatment from some," Wofsy laughs. "They might nod in the hall, but that was all. You know what it was that bothered them—even the guys who were in the antiwar movement with me? It was that I mentioned Bechtel and Chevron." In talking about closed-door negotiations between universities and industry, in which cash is exchanged for special privileges, Wofsy had disclosed the previously hush-hush fact that the university was at that time dickering with the two companies. "They saw that as an act of disloyalty," says Wofsy. "But that's the whole point. The faculty most directly affected by the Engenics deal were never asked for an opinion. We read about it the next morning in the *Daily Californian*."

Support for Wofsy's views seems to vary according to the stock portfolio of the scientist queried. Thus, Professor Keith Yamamoto, a microbiologist at UC San Francisco who watched Genentech's growing pains from a disapproving distance, believes in a clean break: if you want to go into business, fine—then leave the university. "We essentially lose the people who are involved in the companies, anyway," he believes. "Their attention and energy get drained off." But another member of Yamamoto's department, John Baxter, couldn't agree with him less. "Keith Yamamoto doesn't have firsthand business experience. If he did, he'd know the problems aren't excessive." Baxter is helping to start a new firm, California Biotechnology, Inc., with $5 million already in hand through an E.F. Hutton venture-capitalization plan.

If anyone should have hard feelings about cutthroat competition from business, Baxter is the candidate. In 1979 he co-led a UC San Francisco team that synthesized human growth hormone (HGH), a substance used in the treatment of certain forms of dwarfism and previously available only from the pituitary glands of human cadavers. But Baxter found himself in competition with Genentech when a lab member left, taking valuable clones with him. The two groups ended up issuing crosstown press releases on the same day, both claiming victory in the HGH derby. After a legal skirmish, Genentech paid the university $350,000 and a royalty for the work. However, Baxter points out, none of this has interfered with subsequent exchanges. "Sure, we had a discussion at the time," he says, "but the person involved and I are still good friends. We socialize." As for Yamamoto's worry that professor-entrepreneurs give priority to business over university duties, Baxter denies that it's an insurmountable problem. "Among the people I know who have equity, I don't notice any difference."

Still, the strain on the old ethic of free communication is evident. Experimental protocols and lab refrigerators are locked up these days. At a recent meeting of the American Society of Microbiology, a vice president of Exxon advised scientists on the speaking agenda to have their contributions notarized before showing up. Graduate students at Stanford and UC Davis (see box, page 74) have complained about having their thesis topics altered to suit the business needs of their faculty advisers. Friends have become enemies. At Stanford, two of the original founders of Engenics—Channing Robertson and Allan Michaels, both members of the school's top-rated chemical engineering department and former collaborators—barely talk to one another.

THE UNIVERSITIES, AFTER A fashion, have tried to come to terms with the tantalizing prospects of bio-billions. The best publicized of these efforts took place at Pajaro Dunes last March, where, at the invitation of Stanford's Donald Kennedy, the presidents of the nation's five leading research universities—Harvard, MIT, Caltech, the University of California, and Stanford—sat down beside the salt grass and pines of the Monterey coast with officers from eleven corporations to discuss the biotechnology connection. Ironically, the meeting was closed to the press, which, when you consider that the big five chew through over $600 million in federal research and development moneys a year, seemed downright ungracious. Predictably, when the Pajaro privy council came forward with its conclusions, it was showered with criticism from the peeved band of journalists. "Unexceptional principles combined with hortatory language" reviewed the *Washington Post*. If Pajaro Dunes was supposed to reassure the public that the integrity of its research dollar was unsullied by intermingling with corporate funds, the image it projected—a kind of Yalta of the mind, dividing up the future of public health research behind closed doors—achieved the opposite.

The University of California has been laboring the past eighteen months to produce its own bioengineering policy. There appears little prospect it will require professor-entrepreneurs to choose between town and gown, either, and critics say the effort has been narrowly based. Leon Wofsy tells the story of how the selection of a contributing subcommittee took place at Berkeley. "You have to understand," he begins, "committee work in general is one of the banes of a university professor's life, so when a faculty member came around inviting people to help out, they'd put him off. 'Why don't you ask Leon?' they suggested. 'Oh, no!' this fellow answered. 'Leon's too interested.'"

Al Meyerhoff, of the Natural Resources Defense Council (NRDC), a group that has

been bird-dogging the issue of university-industry relations for several years, dismisses Pajaro Dunes as "a smoke screen. It's the classic phenomenon. They feel the hot breath of the reformers on their necks so they try to capture the issue for themselves first, without real reform." Real reform, in Meyerhoff's opinion, would start with disclosure by scientists of their financial interests in business firms that might benefit from government-funded research. Early this year the NRDC convinced the state to require such disclosure when research is privately funded, a decision university spokesmen opposed as a McCarthyist invasion of academic freedom.

Meyerhoff hopes to see the California disclosure language extended to the federal level, as a precondition for federal research grants. "We're not Common Cause," he explains. "I don't care if some university scientist is getting rich. Our concern is that the university plays a vital role in our society. It's our brain trust." With a technology as powerful as recombinant DNA, Meyerhoff wants scientists to be free to ask all the questions and to publicize their findings. "Maybe if we'd been watching the industry connection twenty years ago," he argues, "we wouldn't have DBCP in the wells of the San Joaquin Valley today." (DBCP, a pesticide used to kill nematodes, was shown to cause atrophy in the testicles of rats in the 1950s by a UC San Francisco researcher whose work was funded by Shell, the principal manufacturer of the chemical. Shell delayed publication of the results and never established a "no effect" level for humans. The chemical was banned in 1977 when it was discovered to cause infertility among workers who manufactured it. A recent state health department study points to an increase in stomach cancer among those Californians who unknowingly drank DBCP-contaminated well water over the years.)

The universities' reluctance to be regulated is understandable, and so is their reluctance to crack down on their star researchers. Basic research is a net income producer of significant proportions. For example, the National Institutes of Health awarded California campuses $300 million in research and development grants and contracts in 1981. Of this sum, on average, 25 percent never reached the labs—some $75 million. This money, assigned to a category called "indirect costs," is devoured at the university's administrative level, supposedly to cover the cost of buildings, heat and light, and general overhead. In practical terms, the indirect cost formula means that the researcher who can attract big grants becomes a valuable asset in balancing the books. Max Herrick, a University of Michigan sociologist who has studied the flow of research dollars on campus, summarizes, "The former patron-client relation of the university administration and faculty has been neatly reversed."

But the new hierarchy has clout only so long as the federal government continues to fund life sciences research. President Reagan has shown an inclination to cut back in this area of the budget—some $4.9 billion in 1981. The recent arrival of industry money on campus is a demonstration of Reagan's philosophy that the private sector will take over where the federal government withdraws. But there are consequences. Industry tends to fund applied research—science with a specific goal in mind, a product, such as Merck with its billion-dollar ulcer pill, Tagamet. To nonscientists, this is not an alarming prospect. Inventions appeal to the masses, not knowledge for its own sake. De Tocqueville recognized this fundamental truth about our society when he wrote, "In aristocratic ages, science is more particularly called upon to furnish gratification to the mind; in democracies, to the body." In a sense, then, the last 25 years of more or less steadily increasing support for basic research by the government have been a historical anomaly.

They have also been a shrewd investment. Oddly enough, we always seem to find the best things where we least expect them. Periodically, basic scientists are lampooned for their esoteric noodling in the backwaters of the physical world, and periodically they surprise us with a breakthrough discovery—such as recombinant DNA. By accepting industry money on industry's terms, the university is playing a dangerous game. Private sector investment tends to politicize the process by arousing the fears of public-interest groups like the NRDC. In order to increase the contribution from industry, the research establishment may be hazarding the political support required to fund the other 95 percent of its operation.

This danger is intensified by the appearance that some professors are feathering their own nests with the federal bucks. "I have neighbors who are farmers and mechanics, and they see it pretty straight," says Paul Baumann, a bacteriologist at UC Davis. "They read *Time* magazine. They see that Herb Boyer invested $500 and is now a multimillionaire. His initial research was done in the lab. The capital outlay was from the taxpayers' money."

The ultimate victim, though, is the climate for research. Science is a collective venture—many people working on the same puzzle, their efforts sensible only in the context of one another's work. The rewards of biotechnology, on the other hand, have been distributed in almost Irish Sweepstakes fashion. To some of the winners, this contradiction is an embarrassment. Nobel laureate David Baltimore of MIT, whose share of the great biotechnology lottery is pegged at $2.5 million, admits that the distribution of benefits "seems grossly unfair" but defends it as a necessary part of transferring technology to the marketplace. The example of penicillin is frequently cited. Sir Alexander Fleming did not take out a patent on his idea, preferring to "make a gift" to mankind. Unfortunately, without patent protection, no company would invest in developing it, and as a result

penicillin remained a forgotten laboratory curiosity for almost two decades—until battlefield casualties in World War II drove the government to intervene.

The counterexample to the penicillin story, however, comes in our own time. In 1975, Georges Köhler and Cesar Milstein of the British Medical Research Council Lab discovered how to fuse the skin-cancer cell of a mouse with an antibody-producing white cell. They called the result a "hybridoma," which, when cloned in the test tube, manufactured a pure, specifically targeted disease fighter—the monoclonal antibody. This discovery has become the basis for one of the richest (and most financially promising) areas of immunologic research, despite the fact that Köhler and Milstein decided not to take out a patent. Did he realize the economic importance of the fusion procedure? Milstein is frequently asked. "The answer is yes," he says, "but I do not think we ever guessed at the number of zeros involved in the estimate." The decision not to patent was based on Milstein's perception of a principle. The discovery of monoclonal antibodies, he notes, was an unexpected by-product of pure, basic research, underwritten by the taxpayer. "The practical achievements of science," he contends, "are part of science itself. They are advances in public knowledge and therefore don't belong to anybody, but to society."

This capsulized statement of the once prevailing ethic no longer holds sway. A Stanford graduate student in biochemistry offered this pithy evaluation: "People around here would probably say Milstein was a sucker."

NOBODY WILL EVER SAY THAT about Herb Boyer, although his good fortune, good timing, and talent make him an easy target for just the opposite brand of name-calling. As an assistant professor in the late sixties, Boyer attended nearly every antiwar rally in the Bay Area, absorbing the antiestablishment outlook of the time. Then one day he woke up to discover he had *become* the establishment. He let reporters know he didn't appreciate "all this hype about Wall Street," and eventually he stopped granting interviews altogether. He had always worked hard at science. He enjoyed what he did, but he also thought he had made his own luck. "I've been working at this all my life—that's hardly overnight," he muttered. Besides, the money was incidental. "When the first patient gets treated with something my company makes, that's going to be a very big day for me," he would say.

That day is drawing near. By the end of the year, the Eli Lilly company expects to begin marketing genetically engineered human insulin "somewhere in the world," the first commercial fruits of the recombinant technology. Herb Boyer's prophecy that bacterially produced insulin will cost "ten to hundreds of times less" than that extracted from animals, however, does not appear likely to come true anytime soon. Lilly says it expects to price the protein "at the upper end of the market, in the range of pork insulin." Why so expensive? The company must pay for the $70 million it invested in new production facilities at Indianapolis and Liverpool, England, but that's not an extravagant amount in a $250-million-a-year market. A skeptic might point out that Lilly already dominates the insulin market—no sense in underselling yourself. But company spokesman Ron Culp explains it this way: "The way I look at it, [the price is due to] the new technology that went into it. We've been researching it for years."

A lot of the basic research was funded by taxpayers, of course, but don't hold your breath waiting for royalties. Lilly's insulin monopoly remains intact, because Genentech chose not to fight it. "They had 90 percent of the market locked up. We didn't stand a chance going up against that," explains a Genentech spokesman. However, Genentech *will* receive a royalty for its work. How much? The company isn't saying, but, boasts the spokesman, "It's a very nice royalty."

The bottom line is that diabetics will pay as much as ever for insulin. So where's the great recombinant DNA miracle? "The sale of human insulin is going to do basically nothing for diabetics," answers MIT microbiologist Jonathan King. "It will make a bundle for Eli Lilly and the person who holds the patent." King describes the insulin case as a good example of the public's "having to buy back what it [already] financed."

Nothing is free in this world, certainly not tens of millions in stock. Members of Boyer's old lab team was philosophical about what happened to their mentor. "Herb got more than any scientist can ever ask for," says one. "He made an important contribution, he got recognized, and he became a millionaire. It was hard for him to handle. Science not only requires your mental concentration, it requires your physical presence. He just got distracted."

Boyer continues to run a research lab at UC San Francisco. Six Nobel prizes have been awarded for recombinant DNA research in the last few years, but conspicuously, the holders of the patent—Boyer and Cohen—are not among the laureates. Their mid-1970s work is generally acknowledged as deserving the distinction, but commercialism casts a shadow. "Herb may have lost it for both of them," says a colleague.

The dominant motif isn't envy, surprisingly enough, it's compassion. Says a fellow scientist and old fishing buddy, "Herb really loved science, but the main thing that's happened since Genentech hit it big is that in a sense he's dropped out of the scientific community. You just don't hear about him anymore. He lost his ability to go to people, talk about results, see what's going on. See, when you get tied up with a company, you have secrets. You can't give your competitor the edge. It's not science anymore. You're in business."

July 9, 1982

Dean Charles Hess
College of Agricultural &
Environmental Sciences
Mrak Hall

Dear Charley:

I had recently the opportunity of reading your testimony presented to the House Committee on Science and Technology and would like to make a few comments. I take some issue with the statements that you made in paragraphs 3 and 4 of page 1 where you indicate that it would be great to transfer the Nif gene from the Rhizobia genome to any plant.

Scientifically and biochemically, this is sheer nonsense because what you have to do is literally convert wheat, corn, or rice into a legume and that requires programing these plants to make leghemoglobin, the prerequisite mitochondria to generate ATP, an uptake hydrogenase, transport systems to accumulate molybdenum and iron, and the whole machinery to make the nitrogenase proteins, etc., etc. and the systems to protect these proteins from oxygen.

In support of this statement are the recent comments in Science, 216, 1306 (1982) which state:

> "But the genetics and biochemistry of other traits are much more complex. Genetic engineering of cereal plants to make their own nitrogen fertilizer is often cited as one of the potential payoffs of recombinant DNA technology. This will not happen soon, and for several reasons it may not happen at all. Not the least of the problems is the complexity of the nitrogen-fixing (nif) gene complex of bacteria, which contains some 17 genes. Moreover, no one knows yet how their expression is regulated."

What I am saying is that as Dean of the College of Agricultural and Environmental Sciences, you should not make such simplistic statements to powerful politicians who are non-scientists. Molecular biology is an important tool but I think we should retain an appropriate perspective and not promise to the world a plant that can do everything.

I also feel that we are far removed from a final solution to the industry-University relationship. When you read about the Monsanto-Washington University marriage, one begins to wonder what are the limits of invasion by industry.

Sincerely,

Paul.

P.K. Stumpf
Professor of Biochemistry

PKS/bvg

RESEARCH

UIR Staff

Director *W. Robert Marshall*
Exec. Director *Norbert Hildebrand*
Assoc. Directors *Richard Greiner, George Halldin, George Huber, John Klus, Donald Novotny*

Science Writing Program

Editor *James A. Larsen*
Assoc. Editor *Jean Akhtar*
Graphic Design *Mary G. Jondrow*
Typesetting Data Entry *Kurt Neubor, Ruth Owens*
Contr. Editor *Jean Lang*
Science Writers *Joe Alper, Chris Hamlin, Marc Kennedy, Margaret Patlak, David Pelzer, Lynn Simarski*

Information Services

Director *LeRoy Zweifel*
Asst. Director *Frances Wood*

UIR/Research is produced and distributed by the University-Industry Research Program, Room 1215, 610 Walnut Street, Madison, Wi. 53706.
Unless copyright is indicated for excerpted or reprinted materials, articles published in **UIR/Research** may be used in other publications without specific permission, although credit to **UIR/Research** would be appreciated. Requests for current or past issues should be sent to the above address.

Contents

Vol. 16, No. 1 Winter, 1982

Research

4 **Japanese Industrial Development**

7 **Science, Technology, and Society in the Far East**

9 **New Techniques to Date Old Maps**

10 **Cellular Specialization in Legume Root Nodules**

23 **Integrated Pest Management**

28 **The Lake Trout Story**

32 **Endangered Species**

Industry & Business

15 **Energy Conservation Decisions in Industry**

15 **Transportation Energy Use**

17 **Industry Pursues Methane-Feeding Bacteria**

18 **Let Cad-Cam Do It**

34 **Cost-Benefit Analysis of Road Salting**

UIR Mission

The University-Industry Research Program expedites transfer of useful laboratory discoveries to the marketplace. Competition in many areas of business today is essentially competition between ideas, processes, and devices only a short time removed from the research laboratory. As both international competition and competition from non-Wisconsin industry intensifies, it becomes increasingly important to Wisconsin that results of UW research be generally known and quickly available to state industry.

The industrial liaison program is the heart of the university-industry interaction. Madison campus faculty members—senior faculty from the colleges of engineering, agriculture, and business—work with UIR to initiate and maintain contact with Wisconsin industries. The liaison program 1)marshals UW resources to help Wisconsin companies with research problems, 2)increases the research and development capabilities of Wisconsin industry, and 3)focuses some university research on areas of economic importance to the state.

UIR publications communicate results of UW research to a wide variety of audiences. UIR publishes annually an indexed directory of research on the Madison campus. The information services division of UIR makes available university library and information retrieval services to state industries.

Companies are encouraged to contact UIR staff members when they encounter technical problems. The staff will then work to find specific university resources that could help, such as faculty members investigating the problem area or useful research facilities or equipment. Sometimes discovering an unexplored area suggests a future research need and university and industry together initiate cooperative research programs.

UW-Madison

Part II. Science,
Society, and Technology Series

Japanese Industrial Development

Japan's success is built on an accumulation of factors that go back more than a thousand years.

Jean Lang

"The media likes to suggest that there is some 'single secret ingredient' behind Japan's amazing economic growth," says Solomon B. Levine, chairman of the Department of International Business Research in the UW-Madison School of Business.

"But the truth is Japan's success is built on an accumulation of factors that go back more than a hundred years."

These factors include the nation's history of job allocation, manpower training and labor-management relations. In a recently published book, *Human Resources in Japanese Industrial Development* (Princeton University Press, 1980), Levine and the late Hisashi Kawada have examined the historical development and training of Japan's industrial labor force.

According to Levine and Kawada, the year 1858 was a critical starting point. In that year Japan, still a feudal agrarian economy, signed its first trade treaties with the Euro-American world. As a wide assortment of foreign goods flooded into Japan, the regime foresaw that if Japan did not become an industrial power it would be dominated by other industrial powers. The government subsequently committed itself to modernizing Japan as quickly as possible.

Between 1870 and 1885 the country went through great changes. Among other things feudal institutions were abolished; land tenure was reformed; limits on mobility were lifted; agricultural experiment stations and crop reporting services were set up; nationwide transportation and telecommunications networks were established; foreign teachers and advisers were brought into Japan; and hundreds of Japanese were sent off to Europe and America to learn new technologies.

The Japanese government developed a close relationship with private business, offering subsidies and other incentives to entrepreneurs willing to take a risk on new industries. This close relationship continues to be an important feature of Japanese industry.

World War I accelerated industrial growth and Japan moved into increasingly complex heavy industries such as shipbuilding. When the economic slump of the 1920s hit Ja-

Japan's industrial growth and labor relations are special interests of Solomon Levine.

pan, militarism became a strong force in the country and a policy of colonial expansion was adopted as a cure to the country's economic ills. In the ensuing Pacific war, Japan's industrial plant was left in shambles with more than a third of the country's productive capacity destroyed.

"As the U.S. entered its cold war with the Soviet bloc, it became important to rebuild Japan as an industrial ally," says Levine.

With financial aid from the U.S., Japan put its skilled labor force back to work and plunged into its now celebrated phase of industrial growth. A national policy of "production first" took hold as all resources were poured into building new and diversified industries. Between 1952 and 1972 real GNP grew at a rate of ten per cent a year. The majority of Japanese workers became wage and salary earners by the early 1960s and doubled their per capita incomes. By 1975 incomes more than tripled again.

Training a Labor Force

"In one hundred years Japan went from a feudal agrarian economy —what we might call 'a developing nation' today—to the second most advanced economy in the world," says Levine. "In making this transition the government faced the huge problem of turning a rural agrarian labor force into a force of production workers, technicians, and managers."

The nineteenth century labor market was unorganized and there were few direct links between schools and the new industries. For a time the "patron- client" system filled the gap, a carryover from Japan's agrarian past. Under this system a "patron" contracted to provide and supervise employees for his client. The employee's loyalty lay with his patron rather than with the firm, and the patron and his hirelings could pack up and move on if wages were better elsewhere. As a result job turnover was high and skills training was haphazard.

It was clear that a more stable and better trained labor force was needed. Some industries took on patrons and their retinues as permanent employees. Other firms gradually moved toward a system in which key workers were recruited from schools and given extensive training and seniority privileges in return for a lifetime commitment to the firm.

This system proved successful and over the next 30 years was adopted by many firms. Because key workers with career commitments learned many skills within a firm, they formed a versatile work force that adapted well to changes in technology, production and organization; they had a personal interest in seeing the company prosper; and they had a close working relationship with management.

Because the Japanese government initially left social programs like retirement and unemployment insurance up to the private sector, pension and health plans were slow to develop and social security benefits are still low by western standards.

"The frugality of the Japanese may be more a result of financial insecurity than a devotion to the work ethic," says Levine. "Many unemployed and retired persons must still rely heavily on their own savings, mutual benefit associations, or the resources of their families. The question of how to support a rapidly aging population is a sticky one that lacks a ready answer."

Long-Neglected Problems

Since the 1960s there has been a growing dissatisfaction with burdens placed on society by a "production first" policy. The government has come under increasing pressure not only to eliminate inequalities in income and job security, but also to solve other problems: scarcity of quality housing, overworked transportation systems, air and water pollution, and lack of leisure and recreation opportunities.

"The recent spurt of economic growth has helped to solve one problem. It has dispersed income broadly throughout Japanese society, reaching small as well as large enterprises," says Levine. "Japanese living standards are now equal to those of France, probably are above those of Britain and Italy, but not quite up to Germany and Scandinavia."

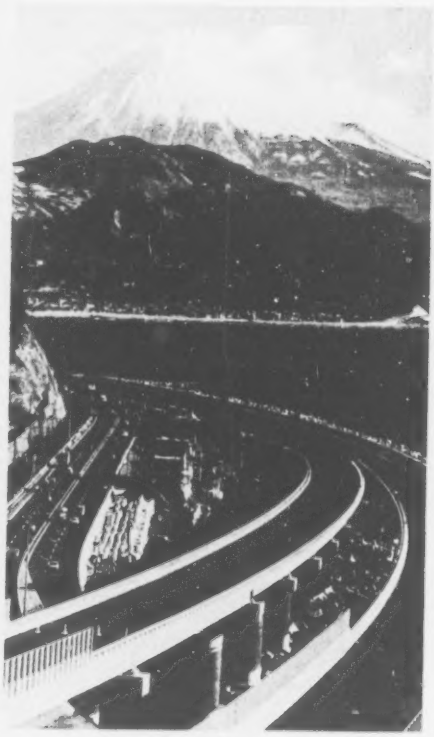
"Other social problems may be harder to solve because they are linked to the incredible rate of urbanization that has accompanied industrialization," notes Levine. "Today 85 to 90 per cent of the Japanese people live in a few areas of flat land abutting the sea—about 115 million people crowded into a space equal to Iowa, Minnesota, and Wisconsin."

At a Turning Point

Although Japan may no longer be enamored of a "production first" policy, production is still a prime concern of the nation.

"Japan is at a turning point," says Levine. "It must decide what industries to get rid of and what industries to expand. A number of Asian and Latin American countries with large la-

One hundred and thirty years ago, Japan was a feudal agrarian society. Today it is a major industrial nation whose economy depends on plants such as the Negishi Oil Refinery in Yokahama.



With land at a premium in Japan's mountainous terrain, auto ownership and the expansion of highways have become controversial issues.

bor forces and abundant raw materials are building up heavy industries like steel and shipbuilding and will soon have a competitive advantage over Japan's aging industrial plants," Levine says. He notes that Japan's textile industry has already started the move to Hong Kong and Korea. Auto manufacturing will probably move offshore to Southeast Asia—to places like Malaysia, Thailand and Indonesia. Singapore could be a candidate to take over parts of Japan's shipbuilding role, he adds.

"Japan is accelerating development of computer systems, and developing new programming and data storage techniques. Japanese have a great interest in 'design for modern living' and would like to become world fashion leaders. These changes call for increased levels of education in the work force, and historically, Japan has done well in meeting these needs."

Japanese economic policy, past and present, is born of a sense of vulnerability says Levine. The Japanese are extremely conscious of their dependence on imports of raw materials, fuels and food. Usable land, particularly arable land, is scarce in this mountainous country and more than 25 per cent of the nation's food supply is imported.

"Because of this vulnerability, the Japanese have developed a broad world view," explains Levine. "They see themselves as international traders serving the world community. They have devloped this role by promoting detente with everybody; by promoting free trade; by furnishing aid and technical assistance, especially in Southeast Asia; and by spending very little money on armaments. Their whole diplomacy is based on not getting involved in conflicts with anyone; they want to be politically independent of all nations and to have good trade relations with many nations."

An Interest in Japan

Levine's interest in Japan dates back to 1942 when the U.S. Navy sent him to the Navy Oriental Language School in Boulder, Colorado. He subsequently served in the Pacific and with the Allied Occupation Force in Japan.

"I have been fortunate in having good able counterparts in Japan and in having good students, both American and Japanese, who have provided an important network for information and scholarship.

"But I am disappointed in the continuing ethnocentricity of American universities. We have focused our studies on ourselves and Europe and have neglected the modern nations of the East—their cultures, history, languages."

"Now we are suffering the consequences of that neglect. We suddenly realize that Japan and other eastern countries are modern nations and we are neither prepared to understand their cultures nor to communicate with them," says Levine. "This is a serious gap in our educational system."

Science, Technology, and Society in the Far East

China plans to use new technology and new processes to increase productivity.

Marvin DeVries
College of Engineering

(In fall, 1980, Professor and Mrs. Marvin DeVries began to plan a trip under the auspices of the People-to-People Citizen Ambassador Program. They had been asked to find a compatible group of manufacturing engineers interested in the manufacturing capabilities, economy, and social structure of The People's Republic of China, Hong Kong, and Japan. "It was an exciting challenge, and we were able to gather together a group of 36 people, all having the same broad interest in foreign cultures and anxious to have the opportunity to study manufacturing and institutions and methods in the Far East." The report that follows is condensed from the Journal: People-to-People Manufacturing Delegation to China, Hong Kong, and Japan, March 2-22, 1981, *prepared by DeVries and other members of the delegation).*

We acquired an understanding of the enormous problems of the Chinese people and the tremendous accomplishments of the Japanese manufacturing community in the past three decades.

We came away impressed overall with their respective cultures, their manufacturing accomplishments and potentials, and the great hospitality of the Oriental peoples. We can learn much from them.

During the period 1966-1976, the time of the cultural revolution, there was chaos in segments of the Chinese economy. Starting in 1979, however, a program of readjustment was begun. There was emphasis on

- Reduction in expenditures on national defense.
- Increasing agricultural production and expanding the consumer-products industries.
- Increasing production through new design, new technology, new processes and technology transfer.
- Economical consumption of energy.
- Insuring stable basic commodity prices.
- Attaining higher quality of life for the people; better housing, clothing, food, and recreation.
- Strengthening management throughout China's entire economy.

In China there are more than 300,000 enterprises in towns, not counting those in rural areas. There are more than 5 million scientific and technical personnel. The number involved in machine tools is equal to that of Japan, but Chinese productivity is much lower. China plans to restructure and increase productivity through reliance on new technology and new processes, better organization and utilization of both labor and management.

In short, the goal of China's program is to strengthen economic efficiency, improve the image of socialism, bring revenues and expenditures into balance, and raise production. It is felt that under the guidance of a socialistic economic plan, China should allow the market to play its role but what model will be best for China is a matter still under much discussion. They want to find a model that requires lower capital investments but which results in greater productivity.

The Chinese note that

- The economy on the whole is good.
- The aim is to make significant progress.
- Trade between the United States and China has increased, as has that between China and Japan.
- Some major problems exist but these can be solved.

China is currently working on its sixth five-year plan which will run from 1981 to 1985. The plan is to emphasize economic and social development, with a low priority on heavy industry and medium priority on the machine building industry. They are pushing for a balance of technical and social development.

Increased production, they explain, will raise the living standard of the nation as well as enhance the quality of life. Their goal is to become a major industrialized nation by the end of this century, thus considerable emphasis is on development of science and technology.

Science and Technology

Scientific research is being conducted in three broad fields: basic, applied, and social. There are more than 2,000 state supported research establishments. Basic research is conduct-

ed in mathematics, chemistry, natural sciences, and astronomy, as well as in engineering and the social sciences. There are five types of organizations carrying on this research:

- The Chinese Academy of Sciences and the Chinese Academy of Social Sciences.
- Government councils or ministries. There are 50 of these, each with its own research units.
- University research institutes.
- Each of the 21 provinces, five autonomous regions, and three municipalities has its own research institutes.
- The national defense establishment has more than 1,000 research institutes.

The Chinese Academy of Sciences is involved in natural science and technology while the Chinese Academy of Social Sciences is involved in basic research in the social sciences. This complicated system of many research institutes introduces some very difficult coordination problems, and it has been suggested that perhaps the two academies should be combined to meet the needs of economic reconstruction.

The government supports basic research. Industry and the municipalities fund applied research and development. China is rich in natural resources, but much exploration and development is necessary to find and use them.. There is strong consumer demand for durable goods such as television sets, recorders, watches, sewing machines, bicycles, and so on.

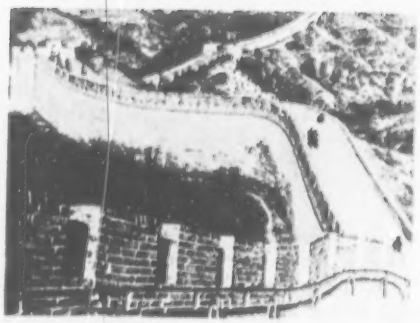
Steel and heavy mechanical industries are being reorganized to meet these demands. China does not plan to export many durable goods, and machine tools will be built for internal use with few for international markets. The need for direction in research and development to support economic reconstruction is apparent. The State Science and Technology Commission is responsible for the important projects. Each year the director of planning for the commission supervises some 400 to 500 major projects himself. Other ministries at the state level and local science and technology units have another 2,000 major projects.

China spends about 1 per cent of its gross output of agriculture and industry on research and development, as compared to 2½ of the gross national product spent for the same purpose in the United States. China has no direct equivalent to the GNP figure of the United States, thus it is difficult to arrive at direct comparison; moreover, China's 1 per cent investment does not include private expenditures for research and development. China does, however, consider its current expenditure sufficient for its purposes at present.

China would like to promote scientific and technological exchange programs with foreign countries, particularly the United States and Japan. They would like to promote increased trade with these countries, but it would seem that if they are serious about this policy they will have to find a way to cut through some of the red tape involved in doing business with them.

Future Policy

The Chinese stress self-reliance, plan to develop their own technical manpower, and expect to be able to develop their own technical knowledge. They do not plan a closed-door policy. They will continue to import new technologies. Currently,



The Great Wall of China

China has 17 agreements of mutual benefit signed with the United States. They will move slowly and take one program at a time since they are not set up to handle large volumes of contracts.

China's 970 million people are divided into 80 per cent rural and 20 per cent urban. Some 40 per cent are employed, with nearly 400 million people in the labor force. Many labor intensive activities could be improved by modern technology, but what to do with the labor that would be replaced?

The oil industry, which inherently is not labor intensive, will use new technology extensively. China's policy, however, is to use appropriate technology where it is needed, but not to over-do-it: they think, for example, "Thermos bottle design has been the same for 50 years, it's a good design, why change?"

The United States policy of peer review has been instituted at the State Science and Technology Commission. Important research projects are carried out under contract; the institutes do research and report to funding agencies. The institutes develop prototypes and demonstrations, and if these prove successful they are taken over by the State Economic Commission for implementation in industry.

(Next: a visit to the Machine Tool Research Institute at Miyun, Beijing)

New Techniques To Date Old Maps

Beta radiography and scanning densitometry probe watermarks in old paper.

John Treacy

Map of the port of Genoa, Italy, published in Rome in 1581.

Space-age research techniques are now being used in the history of cartography to identify the origins and publishing dates of old maps.

Employing beta radiography and scanning densitometry, research tools used in such disparate disciplines as botany and satellite imagery interpretation, geographer David Woodward of the University of Wisconsin-Madison, examines watermarks in map paper to establish the dates when sixteenth-century Italian maps were produced.

Between 1550 and 1570, Italy produced more maps than any other European country, and the city of Venice was Italy's most active map-making center. Hence, the historical importance of Venetian maps and map-making processes has been stressed by scholars interested in the early European map trade.

An approach developed during the past few years by historians is the study of map paper watermarks. By establishing the sequence in which individual sheets were made, determined by examining watermarks, the dates of the maps can be inferred.

"This, however, entails reconstructing how a sixteenth-century Italian paper mill functioned," says Woodward.

Fortunately, information exists to do so. A watermark was made by fastening a thin wire outline of the motif on the transverse wires and vertical chain lines of the paper mold. Dipped into a pulp vat, the screen-like mold was used to form individual sheets, and after pressing and drying, the resulting paper would bear the image of the wire watermark.

Since the operation was performed in a tandem fashion, two molds with twin watermarks of the same design were often used in preparing a batch of paper.

"This process is so well understood," Woodward explains, "that we can discern how the watermark might become altered through time."

Inevitably, the wire form becomes distorted with use. The small knots fastening the design to the chain lines may loosen, or the entire motif may shift slightly off center as the mold is jolted to level the pulp, separate the formed paper, or brushed to remove residue pulp.

(Continued on page 27)

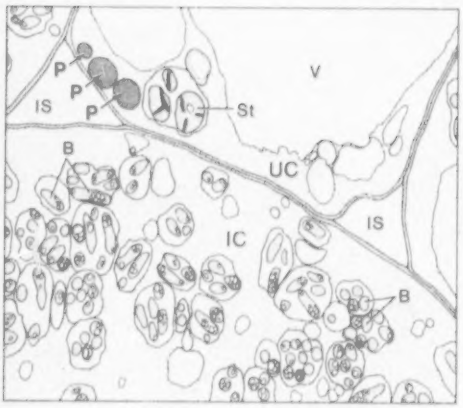
UW-Madison

Cellular Specialization in Legume Root Nodules

A New Kind of Peroxisome

Eldon Newcomb

Department of Botany
University of Wisconsin-Madison



Cover Photo *An electron micrograph showing parts of rhizobia-infected and uninfected cells in the central region of a soybean root nodule. Magnification X 13,000.*
Drawing *The features identified in the drawing include* **B**, *bacteroids in vacuoles;* **IC**, *infected cell;* **IS**, *intercellular space;* **P**, *peroxisome;* **St**, *starch deposit in plastid;* **UC**, *uninfected cell;* **V**, *vacuole in cell. From E.H. Newcomb and S.R. Tandon,* SCIENCE **212**, *1394 (1981).*

(Editor's note: The nitrogen-fixing ability of plants is becoming of ever greater importance as world populations grow, natural nitrate deposits are seen to be limited, supplies of man-made nitrogen compounds for fertilizer become more expensive, and the cost of spreading fertilizers on cropland increases. Studies of nitrogen fixation by symbiotic bacteria in the root tissues of leguminous plants are under way in laboratories, university and industrial, throughout the world. One major advance in understanding the processes taking place in legume root nodules during biological nitrogen fixation accomplished at the University of Wisconsin-Madison has been described in this article. Included are electron micrographs revealing the cellular structures involved in nitrogen fixation in root nodules of legumes such as soybean and bean.)

No. 1. *This infection thread filled with bacteria* (RHIZOBIUM JAPONICUM) *has penetrated into a cell in a young soybean root nodule. At about this stage bacteria break out of the thread and form numerous bacteroids in vacuoles throughout the host cell cytoplasm. X 11,000*

Some recent research on soybeans and other legumes at the University of Wisconsin-Madison campus is shedding new light on the pathway followed by nitrogen after it is taken from the atmosphere and fixed by bacteria in the root nodules.

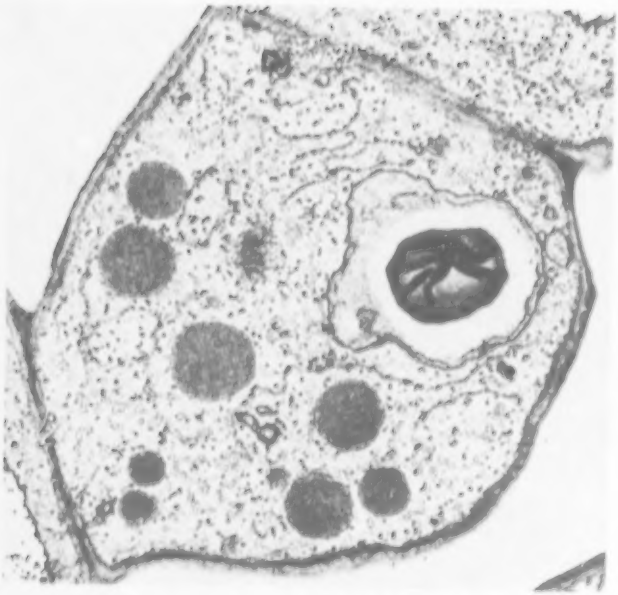
In the last few years, it has been discovered, particularly in laboratories in the United States, Australia, and Japan, that soybeans, beans, and cowpeas belong to a group of legumes known as ureide transporters because the nitrogen fixed by the bacteroids (bacteria in the host cells of the nodule) is largely converted in the nodules to allantoin and allantoic acid, two compounds that together are known as ureides.

These nitrogen-rich ureides are then transported from the roots to the upper parts of the plant, where they are used in growth and especially in seed production.

Soybean and the other leguminous ureide transporters are believed to be of tropical and subtropical origin, while most of the other common grain legumes and the forage legumes are of temperate origin. Temperate legumes transport the fixed nitrogen in the form of asparagine, the amide of aspartic acid.

Production of the ureides requires additional metabolic steps beyond those that are carried out in the synthesis of amino acids and amides by the temperate legumes.

Why the tropical grain legumes like soybean have evolved the extra steps leading to ureide production is not clear. Possibly it is ad-



No. 2. *Several large, spherical peroxisomes are conspicuous in this uninfected cell in a soybean root nodule. The large dark body surrounded by a clear space is a starch grain in a plastid. X 14,000.*

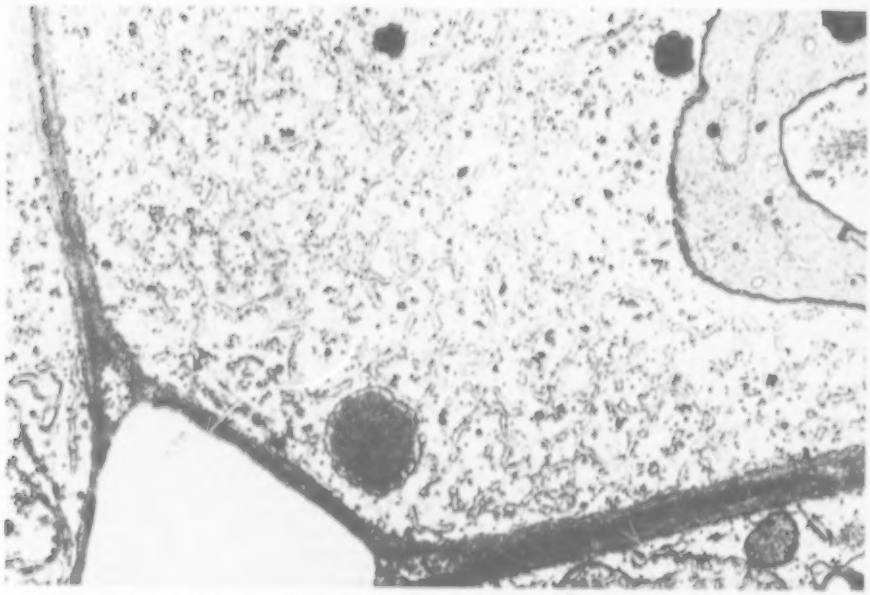
vantageous because formation of the ureides requires less carbon for the transport of the same amount of nitrogen, since in the ureides the ratio of carbon to nitrogen is 1:1, whereas in the amides asparagine and glutamine, the C:N ratio is 2:1 and 5:2, respectively.

In a recent article in *Science*, S.R. Tandon, of the University of Wisconsin-Platteville, and I present evidence strongly suggesting that one of the key steps in the formation of the ureides in soybean takes place in intracellular organelles called peroxisomes (also known as microbodies). Two enzymes involved in a late stage of ureide production—uricase and catalase—are believed to be housed in these root nodule peroxisomes.

We found further that the peroxisomes have an unexpected and surprising location in the soybean root nodule. Like other root nodules, the soybean nodule has on the outside a cortex several cells thick that encloses a central zone of greatly enlarged cells infected with the *Rhizobium* bacteria. Within this central region, for reasons not understood, about half of the plant cells do not become infected by bacteria.

The peroxisomes do not develop in the infected cells as might be expected, but in the uninfected cells (see cover photo). The cells infected with bacteria remain devoid of peroxisomes.

99-177 O - 82 - 13



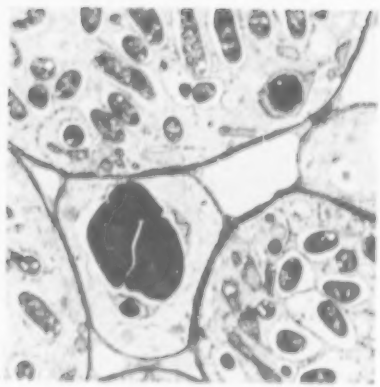
No. 3. *The network of tubules in this uninfected cell of a soybean root nodule is known as smooth endoplasmic reticulum. It is of relatively infrequent occurrence in plant cells. X 28,000*

The development of numerous enlarged peroxisomes is only one of several changes that occur in the uninfected cells of the young root nodules. A rapid proliferation of a second component—known as smooth endoplasmic reticulum—also takes place in these cells and is considered significant because it may be the site where the ureide that is produced in the peroxisomes (allantoin) is converted in part into the second ureide (allantoic acid).

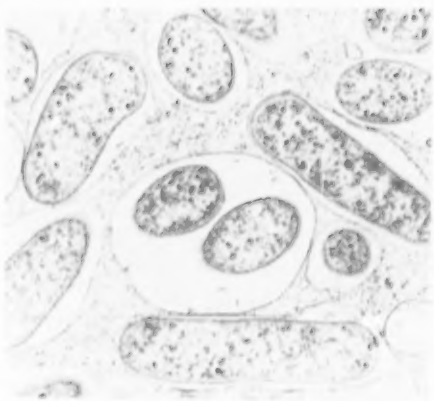
We explain the involvement of the uninfected cells in the symbiosis between bacterium and host as follows: After the nitrogen from the soil atmosphere has been reduced to ammonia by the bacteroids, several of the subsequent steps in the formation of the ureides take place in the infected cells, but compounds formed later in the metabolic sequence move into the uninfected cells, where the final steps in ureide formation take place.

We believe that the infection process causes the uninfected cells to differentiate in a highly specific way so that they become equipped to play an essential role in the nodule. This implies that there is a previously unrecognized specialization of function in the nodule central tissue.

Results on other legumes support the above findings. Bean and cowpea, which also produce ureides for export from the nodules,



No. 4. *In this section through a bean root nodule an uninfected cell (with a large electron dense starch deposit) is surrounded by infected cells. The intercellular spaces (open areas between the cells) facilitate aeration and gas exchange in the nodule. X 6,000*

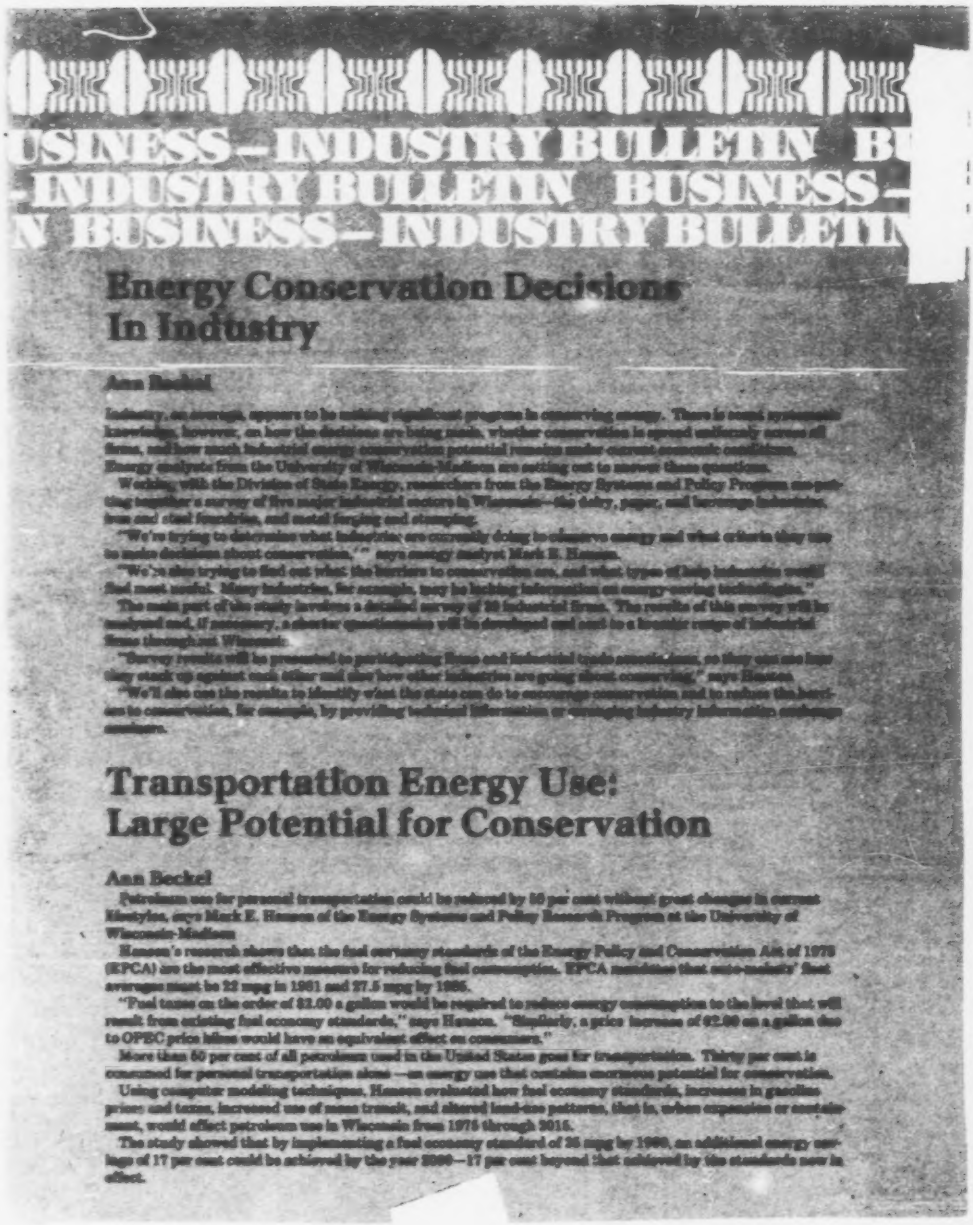


No. 5. *A few bacteroids within vacuoles are seen here in a cell of a bean root nodule. X 13,000*

resemble soybean in containing many uninfected cells in the central infected region of the nodule. In both legumes, the uninfected cells undergo the same ultrastructural changes in the developing nodule that are seen in soybean, including the formation of numerous large peroxisomes and of smooth endoplasmic reticulum.

On the other hand, in vetch, an asparagine transporter, there are relatively few uninfected cells, and these cells are completely lacking in peroxisomes. Presumably in vetch the uninfected cells play little or no role in the metabolic transformations of the recently fixed nitrogen.

Before their discovery in legume root nodules, peroxisomes were known to play an important role in only two other plant tissues. In the leaves of plants, numerous large leaf peroxisomes occur in close association with chloroplasts and mitochondria, and participate in photorespiration. In the fat-storing cells of germinating fatty seedlings, peroxisomes known as glyoxysomes participate in an important way in converting fat to carbohydrate. The nodules of the ureide-forming legumes appear to represent a third location in which plant peroxisomes play a prominent metabolic role.



USINESS—INDUSTRY BULLETIN BU
-INDUSTRY BULLETIN BUSINESS-
N BUSINESS—INDUSTRY BULLETI

Energy Conservation Decisions In Industry

Ann Beckel

Industry, on average, appears to be making significant progress in conserving energy. There is scant systematic knowledge, however, on how the decisions are being made, whether conservation is spread uniformly across all firms, and how much industrial energy conservation potential remains under current economic conditions. Energy analysts from the University of Wisconsin-Madison are setting out to answer these questions.

Working with the Division of State Energy, researchers from the Energy Systems and Policy Program are putting together a survey of five major industrial sectors in Wisconsin—the dairy, paper, and beverage industries, iron and steel foundries, and metal forging and stamping.

"We're trying to determine what industries are currently doing to conserve energy and what criteria they use to make decisions about conservation," says energy analyst Mark E. Hanson.

"We're also trying to find out what the barriers to conservation are, and what types of help industries would find most useful. Many industries, for example, may be lacking information on energy-saving technologies."

The main part of the study involves a detailed survey of 80 industrial firms. The results of this survey will be analyzed and, if necessary, a shorter questionnaire will be developed and sent to a broader range of industrial firms throughout Wisconsin.

"Survey results will be presented to participating firms and industrial trade associations, so they can see how they stack up against each other and also how other industries are going about conserving," says Hanson.

"We'll also use the results to identify what the state can do to encourage conservation and to reduce the barriers to conservation, for example, by providing technical information or managing industry information exchange seminars.

Transportation Energy Use: Large Potential for Conservation

Ann Beckel

Petroleum use for personal transportation could be reduced by 50 per cent without great changes in current lifestyles, says Mark E. Hanson of the Energy Systems and Policy Research Program at the University of Wisconsin-Madison.

Hanson's research shows that the fuel economy standards of the Energy Policy and Conservation Act of 1975 (EPCA) are the most effective measure for reducing fuel consumption. EPCA mandates that auto makers' fleet averages must be 22 mpg in 1981 and 27.5 mpg by 1985.

"Fuel taxes on the order of $2.00 a gallon would be required to reduce energy consumption to the level that will result from existing fuel economy standards," says Hanson. "Similarly, a price increase of $2.00 on a gallon due to OPEC price hikes would have an equivalent effect on consumers."

More than 60 per cent of all petroleum used in the United States goes for transportation. Thirty per cent is consumed for personal transportation alone —an energy use that contains enormous potential for conservation.

Using computer modeling techniques, Hanson evaluated how fuel economy standards, increases in gasoline prices and taxes, increased use of mass transit, and altered land-use patterns, that is, urban expansion or containment, would affect petroleum use in Wisconsin from 1975 through 2015.

The study showed that by implementing a fuel economy standard of 35 mpg by 1990, an additional energy savings of 17 per cent could be achieved by the year 2000—17 per cent beyond that achieved by the standards now in effect.

Hanson also found that doubling the use of mass transit would reduce auto emissions in urban centers, but would reduce state-wide use of petroleum only a few percentage points because of the very low rates at which Wisconsinites have used mass transit in the past.

Policy Recommendations

Hanson's research produced a number of recommendations for federal, state, and local transportation policies. He maintains that in addition to adopting a 1990 fuel economy standard of 35 mpg, two deficiencies in the EPCA fuel economy standards should be corrected.

"Environmental Protection Agency ratings overstate actual fuel economy, so the energy saving is less than what would be achieved if the ratings were accurate.

"Moreover, a large class of vehicles, including pick-up trucks, vans, and 4-wheel drive recreational vehicles, have been excluded from the federal automobile standards. The use of these vehicles for personal travel—as opposed to commercial, freight, and farm purposes—means that energy use for personal transportation is roughly five per cent higher than it would be if they achieved the same fuel economy as the rest of the auto fleet."

Despite finding that very high taxes would be required to reduce fuel consumption, Hanson recommends that Wisconsin increase the existing tax on gasoline and diesel fuel and set the tax as a percentage of market prices.

Increasing taxes would provide badly needed funds to maintain the existing transportation system and would also affect those vehicles currently excluded from the federal fuel economy standards, Hanson explains.

He further recommends that Wisconsin implement registration fees that, for new vehicles, increase with the fuel consumption per mile.

"The costs of automobile use should be borne by the users," says Hanson. "Those costs go beyond maintaining streets and highways which are not fully paid for by users. It's estimated that more than 50 per cent of court and police costs are related to auto use.

"There is a more subtle, but important cost to consider—20 to 30 per cent of most cities' land area is under streets and parking lots. That land is unavailable for other uses and is no longer taxable."

Barriers to Conservation

Hanson contends that the major problem in developing effective transportation policies is that consumers have been getting conflicting signals. Fuel economy standards tell them to conserve. But in constant dollars, fuel and auto prices have been declining for the past 20 years, and only with the 1973 embargo did fuel prices return to the 1955 level. The increases of 1979 and early 1980 pushed real prices significantly above 1955 levels.

Historical trends in fuel and auto prices and increases in real per capita income, combined with the large investments made by the state and communities in highway construction strongly encouraged auto use and urban sprawl, says Hanson.

"The state should get out of the business of providing high-speed, limited-access highways to the doorsteps of people who choose to live 15,20, and 30 miles from their jobs, and instead provide an efficient, easy-access transportation system within cities that makes it convenient for people to live close to their jobs."

Hanson strongly recommends that Wisconsin's transportation policy include development of safe bikeway systems for bicycles, mopeds, and 3-wheel bikes that can be used for carrying groceries and other goods.

"Sixteen per cent of U.S. auto miles are for trips less than five miles in length and yet these trips consume 31 per cent of the fuel. Many of these short trips could be made by bike if people had safe and convenient bikeways."

Unpopular Policy Options

Policy options to reduce transportation energy consumption are politically unpopular. In general, the greater the energy impact the greater the opposition, says Hanson.

"Until a couple years ago, auto-makers opposed the fuel economy standards and crusaded to get rid of them. But demand for small cars increased so dramatically in 1979 that none of the auto-makers is now having trouble meeting the standards.

"With the current anti-regulatory mood in Washington, however, it's very doubtful that any new standards will be imposed."

Hanson points out that EPCA forced the auto industry to design small cars in the mid-1970's.

"It takes four to five years to come out with a new model. If auto-makers had waited to design small cars until the increased demand for them in 1979, American-made small cars would not have been available until 1983, and the Japanese would have really captured the market."

Many policy recommendations, such as gas tax increases and increased registration fees for energy inefficient vehicles, are opposed because people think they will have negative impacts on the auto and tourism industries. But Hanson contends that U.S. experience since the 1973 embargo shows that inadequate fuel supplies and a failure to match fuel demand and supply at a given price are far more damaging to those industries.

99-177 O - 82 - 14

Increasing gasoline prices have brought about a surge of interest in conservation. So why not simply rely on the marketplace to solve the problem of petroleum shortages?

"Some conservation is being brought about by market mechanisms. But liquid fuels are so important to this nation's economy that I'd like to see government conservation policies maintained and in some instances further developed to guarantee that conservation takes place," says Hanson. "Moreover, there is no free market for some services such as highways and bicycle lanes."

"Some individuals can afford to drive cars with low fuel economy regardless of gasoline prices. Should the country be saddled with problems of liquid fuel shortages or the threat of import cut offs because of these drivers?"

Methane-Feeding Bacteria Hotly Pursued by Industries

Ann Beckel

Methane-oxidizing bacteria are provoking visions of dollar signs. Called methylotrophs, the bacteria "feed" on methane, the principal component of natural gas.

The methane-feeders have two characteristics that make them highly useful to industries. The enzymes the bacteria use to break down methane insert oxygen into methane and methanol. The enzymes are also highly nonspecific; that is, they insert oxygen into not only methane and methanol but do the same to hundreds of other chemicals as well.

"Using current chemical processes, it is very difficult to insert oxygen into specific sites on several compounds. Enzymes that can do this will have tremendous value to industries," says bacteriologist Richard S. Hanson of the University of Wisconsin-Madison.

Moreover, the enzymes can remove chlorine from chlorinated hydrocarbons, which makes them potentially useful for detoxifying many toxic pesticides and industrial solvents and plasticizers.

Discovered in 1975

Methane-oxidizing bacteria were known to exist as early as 1906. But before 1975, the existence of facultative methylotrophs—bacteria that can use more complex chemicals as well as methane for growth—was widely doubted.

"We discovered facultative methylotrophs in 1975, and since then they've been found in every natural environment investigated from flower gardens to fresh waters," says Hanson.

A number of industries interested in the methane-eaters have contacted Hanson, and he is currently investigating ways to exploit the bacteria's remarkable abilities for industrial purposes.

Hanson and graduate students working with him have found that the genes for the enzymes that break down methane are on plasmids, small portions of genetic material that exist outside the primary genetic material in the bacteria.

"Parts of the plasmids can be cloned and the enzyme-producing genes transferred to organisms more suitable for industrial processes, that is, to bacteria that are easier to grow and maintain, for example," Hanson explains.

Using recombinant DNA techniques, the scientists hope to produce organisms that manufacture greater quantities of the enzymes.

"We're currently the only ones who have a methylotroph genetic system usable for gene transfer and recombination," says Hanson. "We also have mutants that can be used to study and map the genes responsible for producing the enzymes."

Productive Active Sites

Only a very small part of the enzyme molecule—the active site—is actually involved in reactions. The enzyme is like a large house with a lock. The compound to be broken down by the enzyme fits into the "lock"—the active site—rather like a key, and the reaction proceeds. The active site can be used over and over again.

If the scientists can isolate and characterize the active site, it may be possible to produce and use the "lock" without having to produce and maintain the rest of the "house"—the entire enzyme molecule.

Bacteria are not the only organisms that use methane. Holly Wolf, who worked with Hanson as a graduate student, has isolated and studied methane-feeding yeasts.

"There are advantages to using yeasts rather than bacteria in many industrial processes. Yeasts are easier to handle," explains Hanson. "So far, however, methane-using yeasts have been very difficult to study because they grow so slowly. We're now trying to find naturally occurring yeasts that grow faster and produce more of the enzymes."

No commercial products made by processes using methane-feeding organisms are currently on the market. But various industries have applied for about 20 patents for processes using either the bacteria or the enzymes. Scientists and industrialists alike seem confident that these humble organisms have an important role to play in industries of the future.

Computers Revolutionize Engineering

Let Cad-Cam Do It

Jean Lang

Life is easier for engineers since CAD and CAM came on the scene. CAD (computer-aided design) and CAM (computer-aided manufacturing) are applications of computer science to a wide variety of jobs—from preparing blueprints and organizing assembly lines, to programming robots.

"Ten years ago the costs of CAD/CAM were prohibitive to all but the biggest manufacturing firms," says John J. Uicker, Jr., director of the College of Engineering's Computer Aided Engineering Center. "But today a system that once cost millions is available for about a hundred thousand dollars—an investment that many industries can afford. As a result, business is clamoring for more CAD/CAM equipment and programs, and for more engineers trained to use them."

Uicker adds that computer-aided design, in particular, holds great promise because it can meet a variety of design needs in many industries. At the heart of CAD is "interactive computer graphics," a system that combines a computer terminal and keyboard with a cathode ray tube (much like a television screen) on which three-dimensional images as well as data can be graphically displayed. The system is called "interactive" because an engineer can interact with the computer, through graphics, to work out problems.

"For example, if you want to alter the dimensions of a machine part which you have programmed into the computer, you punch in the new dimensions and the graphic display immediately reconstructs itself to show you the new shape. If that's not exactly what you wanted, you can change the design by additional data manipulations."

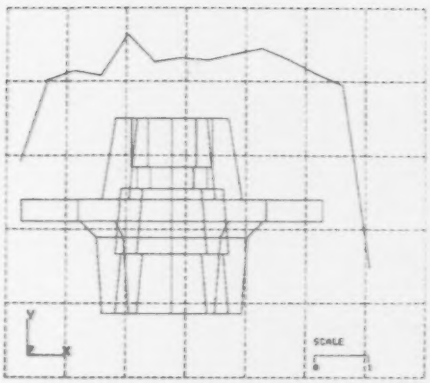
The obvious advantage of CAD is the elimination of time-consuming and tedious tasks such as drawing and redrawing a design or combing through stacks of blueprints to find pertinent data.

In response to concerns that CAD will displace traditional design staffs, Uicker points to the banking industry which has become completely computerized without significant job loss. "Rather than spending time doing hand calculations, bank personnel have time for more creative money management."

"Or," he says, "consider this example from my own experience. I worked for a year with Ford Motor Company setting up a CAD program for the design of suspension systems. I was later told that the program had saved Ford 100,000 man-years of drafting board time. What they meant was the CAD system allowed engineers to look at a thousand times more design possibilities than would have been possible using pencil and paper. Bringing in a CAD system did not result in fewer workers at Ford, but rather better design."

Much to be Learned

While industries are anxious to push CAD/CAM technology into as many phases of their operations as possible, Uicker warns that it will be some time before the various computer-aided systems are well-integrated.



A computer graphic from the CAD cast metals program shows metal solidification time for a particular cross-section of a gear hub.

"CAD/CAM has been developed in a more or less piecemeal fashion to meet the needs of particular groups of users," says Uicker. "There are big gaps in our knowledge. For instance, we really don't know the best way to organize and store data so that it can be tapped for many different uses within one firm.

"There are big questions about how to integrate micro- and minicomputers with the big computers that hold vast amounts of data. Or, how do we transfer data from a computer program designed for 'wire-frame graphics', which depict only the outline of an object, to a program designed for 'solid graphics' which show the solid surface of objects?"

At the manufacturing end of the system also, pockets of expertise are separated by deserts of ignorance. Uicker predicts, however, that in five to ten years the gaps will be filled.

"Ideally, when you sit down at a computer terminal in the future and design a certain diameter hole to go into a piece of metal, the computer will tell you whether you have the machinery to tap screw threads for that size hole. And, if you don't, the computer will tell you what diameter hole can be tapped with the machinery on hand, or how soon a supplier can get the necessary equipment to you. Then, when the design is complete, the computer will relay instructions to your robotized drill press," says Uicker.

CAD/CAM at UW

Uicker and other engineers are developing new CAD/CAM programs as well as devising means to tie the various programs together. Henry Guckel of the Integrated Circuits Laboratory, for example, uses CAD to design new microelectronic circuit patterns and uses CAM to automate the produc-

tion of the actual chips. Andrew Frank in electrical engineering and Norman Beachley in mechanical engineering have used CAD to simulate the operation of a flywheel auto transmission system; and S. M. Wu, also of mechanical engineering, is working with General Dynamics to adapt automatic sensing devices to drill work on aircraft frames.

"Putting together an airplane means drilling about ten million holes," says Uicker. "How well those holes are drilled not only affects the company's productivity but also the structural life of the plane."

Wu is investigating how to control the feed-rate of a drill for optimum performance and minimum wear. He has also designed a computer-controlled drill-point grinding machine. The machine's microprocessor directs the precise grinding of drill points into a variety of geometric shapes from ellipsoidal to conical.

Wu is also helping General Dynamics improve the performance of its hole-drilling robots by fitting out the robots with special "sensor packages." One sensor, for example, monitors the condition of the drill point and prompts the robot to replace the drill when it becomes worn. Another sensor monitors and controls drilling rate during the sensitive "breakthrough" part of the drilling process.

Robotics for Welding

Another long-time leader in CAM, mechanical engineer John Bollinger developed robotics for welding and automated product inspection systems.

Neil Duffie has worked closely with Bollinger and says that cooperative work with the A.O. Smith firm over the past 17 years has led to several important CAM developments.

"A. O. Smith welds automobile frames," says Duffie. "The company wanted to automate the process to increase productivity and to get a uniform quality welded seam. After much experimentation and the design of three prototype machines, a production model finally was built."

The machine, which is computer-programmed, clamps together the parts to be welded. Then, special welding heads begin to move along seams on both sides of the part. A finger-like tactile sensor moves in front of each head "feeling" the contour of the seam and guiding the head along. When the welds are complete, the finished piece is automatically removed from the machine.

This project has had several spin-offs. In developing the welding machine, Bollinger found that the quality of a weld depended on the amount of heat present and the average size of the molten metal drop. Direct measurement of these factors, however, is difficult. Consequently, Bollinger, Duffie, and Norman Bratan are attempting to use other, more easily measured elements of the welding process—like current, voltage, and feed rate of welding wire—to indirectly measure heat and drop size.

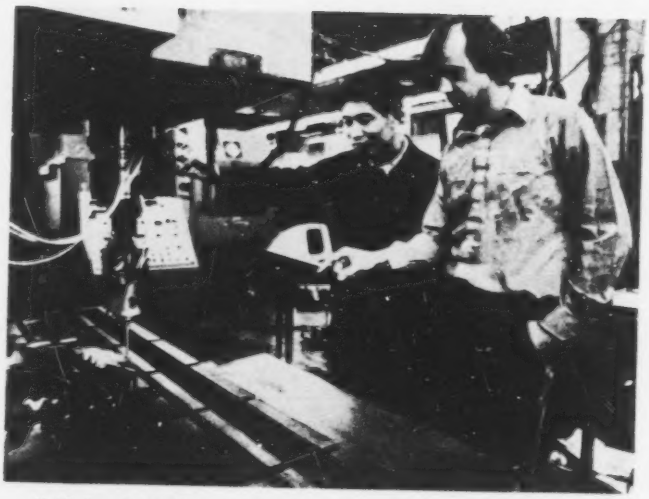
Their goal is to design an automatic feedback system that will continuously monitor machine voltage, wire feed, and current; convert the data into measures of drop size and heat; and automatically adjust the machine to hold drop size and heat constant.

Computer-aided design and manufacturing can serve many industries: from the electronics firm designing minute integrated circuits to this foundry producing massive metal castings.

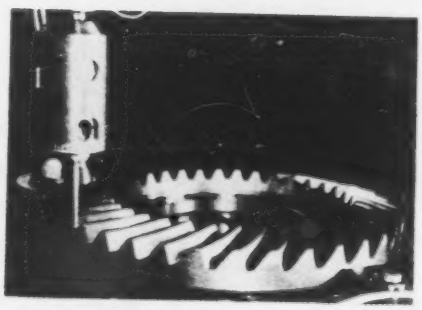
Quality Control of Gears

In another CAM project, Bollinger received a four-year grant from the Gleason Gear Works in Rochester, New York, to develop a method for the automated precision measurement of gears. Bollinger designed a computer-aided tactile probe that slides across the surface of the gear like a ball-point pen, making point to point measurements as it moves. The measurements are processed by an attached micro-computer which ultimately determines whether or not the gear meets quality standards.

"In the process of developing the tactile probe, we realized that it also had application to a number of industrial processes including automated welding and automated tracing machines," says Duffie. "So, we organized a consortium of companies interested in tactile sensing and its application to robots and automated measuring devices. With the support of eight firms, we are working simultaneously on probe development, computerized tracing and automatic welding."



Neil Duffie and visiting Chinese scholar Chao-Zhen Hou watch a computer-aided tactile probe as it automatically inspects a gear.



The tactile probe slides across the surface of a gear, making precise point to point measurements as it moves.

CAD in the Foundry

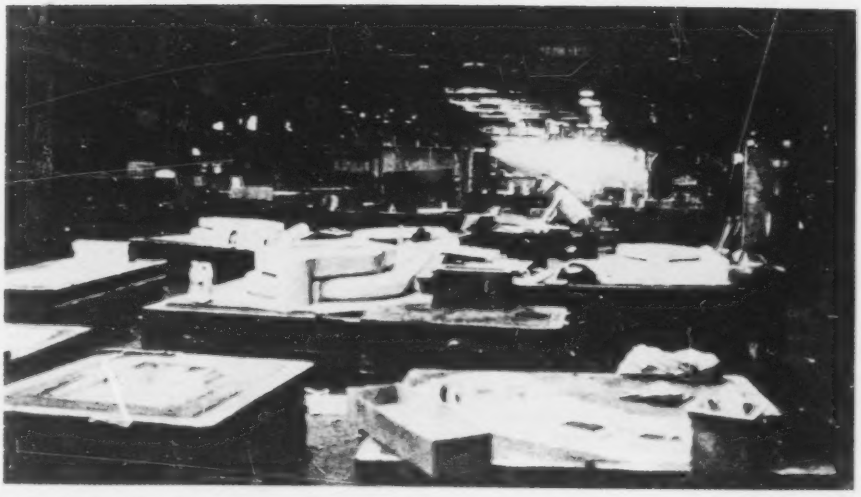
Uicker notes that an industrial consortium has been an important funding source for his own CAD research in metal castings. "Consortia make good sense," he says. "They allow small and medium size firms to fund research that none of them individually could afford to support.

"Our project with several member companies of the United Foundrymen of Wisconsin began about the time we were putting our Computer-Aided Design Center together," notes Uicker. "Larry Kreuger, the chairman of the United Foundrymen, proposed that the various foundries chip in to fund research on the CAD of castings and casting patterns. Prof. Richard Heine and I talked with the foundrymen about the needs of their industry, and we found there were frequent problems in matching job bids with the actual costs of producing a casting."

He explains that when a foundry is invited to bid on a casting there may be only a few days in which to put together an estimate. Because foundrymen can't always anticipate complications that may arise from a particular design, they may seriously underestimate the cost of the job and take a loss. "We agreed to put together a CAD program for the foundrymen that would improve casting design and take some of the guesswork out of bids," says Uicker.

Making Better Castings

The cast metals program is based on geometric modeling. With a digitizing tablet, the blueprint of the casting is traced and the dimensions transferred to a computer. There the cast-



Better castings at less cost and with less waste of metal is the goal of the CAD cast metals program.

ing can be graphically displayed in a series of cross-sections or as a three-dimensional image which can be rotated for a variety of viewing angles.

"The program can also compute the casting's weight, surface area, volume and the percent metal yield per metal poured. Equally important, the program points out casting weaknesses," says Uicker. "Problems can occur if part of a casting begins to cool before all the metal is poured. We have provided our program with the capability of estimating cooling rates of various parts of a casting and to graphically display where these 'hot spots' will occur. This allows the foundry to correct defects in design before a single drop of metal is poured."

"The CAD casting design system has great potential to produce better castings at less cost and with less waste of metal," says Uicker. "It should be especially valuable when dealing with complex castings like engine blocks. And with smaller castings, I wouldn't be surprised if eventually the foundry engineer goes right out to the customer's plant with a portable computer and gives an estimate on the spot."

In the Classroom

Uicker says the CAD program will be used in the metals casting classroom as well as the workplace. The students will use the computer program to design their castings and then use molds and sand to verify their designs with physical results.

"The foundrymen are tickled pink with this program," he adds. "Besides getting direct benefits, they are improving the image of their industry in the students' eyes. Foundries are the fourth largest manufacturing industry in Wisconsin. This program presents foundry work as a worthwhile career and shows the students that they can bring new technology into the foundry."

Industry wants more students like those coming from the CAD cast metals program—students who know how to use CAD/CAM systems creatively. To meet the need, the College of Engineering is undertaking a major effort to increase funding for computer facilities. The goal is to give all senior and graduate students some hands-on experience with CAD/CAM.

"This will require a large investment, one that I belive is essential to keep UW in the forefront of engineering," says Uicker. "The Graduate School has helped tremendously with funds for some initial purchases of computer equipment. We are now seeking additional funds from industries and the National Science Foundation.

"Four years ago," says Uicker, "I wasn't totally convinced that CAD/CAM was here to stay. Now there is no doubt in my mind. It's here to stay and it must become a major thrust of the college."

Mexico City Gasps for Alternatives

Lynn Simarski

The prognosis for Mexico City's air quality looks bleak—but there are practical alternatives, says Mark E. Hanson, systems analyst for the Energy Systems and Policy Research Program, University of Wisconsin-Madison.

The high mountain peaks that surround Mexico City, one of the world's largest urban areas, form a natural trap for air pollution. If the valley's population of about 16 million doubles as predicted by the year 2000, the amount of automobile emissions is likely to follow suit.

Hanson has predicted the future effects of Mexico City's transportation trends on energy use and air quality. His computer model represents the region's transportation network as a system with population, income, and the price of gasoline as inputs, and tons of emissions, energy use, and vehicle miles as outputs. The emissions considered are carbon monoxide, hydrocarbons, nitrogen oxides, particulates, and sulfur oxides.

"Mexico Valley's energy use may be growing by ten per cent annually," Hanson says. "Roughly four-fifths of the polluting emissions are from cars, buses, and trucks. We can predict how much air pollution will result from a specific number of vehicle miles—and show how much the current problem will worsen."

Hanson can also estimate the benefits of reduced energy use. He first constructs a "base case"—the future energy and pollution scenario likely from population trends and other model inputs.

The model is used to calculate the number of vehicle miles, which can then be translated into measures more meaningful for policy makers, such as energy consumed or emissions produced.

Hanson has modelled alternate plans that vary the amount of travel in different modes, such as by car, bus, or subway. He can calculate, for example, how much a greater number of mass transit routes or bicycles would improve air quality in Mexico City.

"We can vary population density or the price of gasoline and see how they affect travel patterns," he explains.

Policy makers might curb air pollution with a number of options, and the model demonstrates the effects of different alternatives. Hanson's research has explored policy paths for automobile travel and mass transit use. In oil-rich Mexico, where gasoline is relatively cheap, the price of cars could restrain energy use.

"Cars could be taxed more heavily or certain streets restricted to bicycles only," Hanson says.

More mass transit is another obvious option for crowded Mexico City.

"Planners want to know how much money should be put into constructing subways," he says. "The model can be used to estimate the effect of this policy on air quality.

"The downtown buses and the subways are now jammed to capacity. More subway routes would save energy and also cut back pollution from buses and cars—because subways are powered from electricity which could be generated by plants outside the valley."

But the model does not just focus on the future.

"We have used the model to assess the effect of the current automobile emission control devices on air pollution," Hanson explains.

If energy use continues to escalate at present rates, according to the base scenario, Mexico City will be guzzling energy at six times its present level by the year 2000.

Hanson says that with some steps toward conservation, however, the jump in energy use could conceivably be cut in half.

Hanson has discussed the results of his analysis with scientists and officials in the Mexican government and universities.

A field scout in Green County inspects for corn rootworm beetles.

somewhat weedy stands. It may be that the weeds provide alternate hosts for these pests or that the weeds are important cover for predatory insects," says Scriber. "We need to verify this finding and determine the causal mechanisms; but should it prove true, it would mean that tolerating some weeds could help reduce certain sucking insect populations.

"But there is a catch," adds Scriber. "At least one group of alfalfa pests, the caterpillars, may increase rather than decrease in weedy stands. Unfortunately, there is no single answer or panacea for all the problems."

Weeds affect insect populations in subtle as well as obvious ways. Weeds compete with crops, depriving them of nutrients and moisture. When the crop is stressed, its feed quality declines, making it less nutritious to insects. While stressed plants may be less acceptable because of lower feed value, they may also become more appealing due to a decline of so-called allelochemics—often toxic chemicals that are built-in insect repellants. The decline can make the stressed plant more vulnerable to both insects and pathogens. Other forms of biological plant stress may however increase allelochemic concentrations with the opposite results.

"Fungicides and herbicides may also influence a leaf's palatability to insects," says Scriber. "We plan to look for the effects of particular weed and pathogen management practices on the insect populations. At the same time plant pathologists will be looking at how different herbicide and insecticide treatments affect levels of plant disease."

Complex Decisions

As more is understood about crop-pest relations, crop management decisions become more complex. Fortunately, farmers don't have to make those decisions alone. They are getting help from UW Extension computerized crop and pest management programs.

With the aid of the USDA, Jeffrey Wyman, John Wedberg and colleagues in other departments have developed computer management programs for potatoes, snap beans, alfalfa, dent corn, and sweet corn—crops which are a vital part of Wisconsin's economy. The programs depend on an environmental monitoring network that provides data on weather, soil conditioning, and other factors affecting crop growth and pest outbreaks. Field scouts, who sample farmers' fields regularly, provide actual counts of pests in the field.

"When this information is analyzed, we get a profile of the pest problem and a set of management options," says Wyman. "Extension offices then get the information to farmers by radio and special telephone tape services."

After the initial development phase of IPM programs by UWEX, growers pay an acreage charge for the scouting service. It is a small investment with a high return," says Wyman. The farmer gets a regular report on crops and helps the extension office develop an up-to-the-minute profile on regional crop-pest interactions.

"Our goal is to turn the operation of pest management programs over to the growers and the private sector" says Wyman. "We will continue to develop programs, assist in their implementation and operation, train the field scouts, and coordinate the overall effort, but we want the growers to be the prime organizers."

Integrated Pest Management
The Crop as Ecosystem

Natural biological controls can keep pests at tolerable levels.

Jean Lang

"We are trying to get away from the idea that weeds alone, or insects alone, are the problem," says entomologist J. Mark Scriber. "A crop is an ecosystem in which many biological and physical factors are simultaneously at work."

Scriber and his colleagues, entomologists Jeffrey A. Wyman and John L. Wedberg, are advocates of integrated pest management (or IPM). They believe that pests can best be managed by a combination of selective pesticide use and manipulation of biological forces.

"An integrated philosophy was behind all pest management prior to World War II," says Wyman. "However, the war brought major advances in chemical synthesis of insecticides, herbicides and fungicides and everyone swung to chemical management. By the 1970s the shortcomings of chemicals were apparent —increasing costs, persistent environmental hazards and the development of pest resistance," he continues.

"In returning to an integrated approach, we are following the lead of forest entomologists. With the vast acreages that must be managed in a forest, it's impossible to rely on a single approach to pest control," says Wyman. "And since a forest is a relatively stable ecosystem, it is logical—and possible—to put natural biological controls to work, keeping pests at tolerable levels.

"Bringing IPM to agriculture is a little more difficult," he adds. "The agro-ecosystem by its nature lacks stability. With crops as well as pests changing from year to year, it's a challenge to manipulate the ecosystem to advantage."

IPM Consortium

In an attempt to understand pest-crop interactions, Mark Scriber is participating in a sixteen-university project called the Consortium for Integrated Pest Management. The consortium has focused on four major crops—alfalfa, apples, cotton, and soybeans—and each university carries out a particular aspect of research. Funds have been provided by the U.S. Department of Agriculture (USDA) and the Environmental Protection Agency (EPA).

"Wisconsin takes part in the alfalfa subproject," says Scriber. "Team members include plant pathologists Craig Grau (coordinator) and Douglas Maxwell, agronomist R. Gordon Harvey, and myself. Our goal is to get a better understand ing of how different alfalfa pests interact with one another and with the crop at different stages of its development. Specifically, we are looking at the relationship of weeds, insects, and pathogens to seedling establishment, stand longevity, and the quality of the yield."

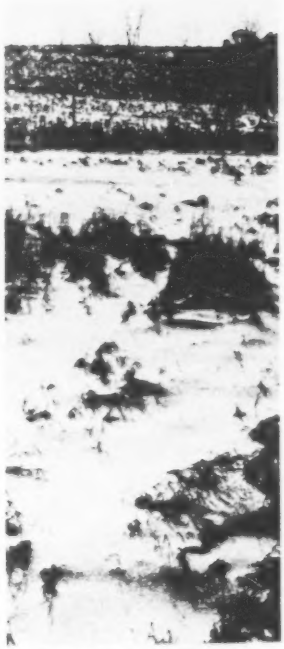
"Some of our preliminary studies show that totally weed-free alfalfa stands can have more aphids, leafhoppers and alfalfa weevils than adjacent

UW scientists are exploring integrated approaches to pest management in alfalfa crops such as this one in Manitowoc County.

Integrated Pest Management
Plant Warfare

"The better we understand allelopathy in weeds the better we can fight it."

Jean Lang



Chemical exudates from certain weed and crop residues may carry over from one year to the next, inhibiting the growth of subsequent crops.

Some plants wage chemical warfare. The war zone is the soil, where chemicals from one species inhibit growth of other species—a chemical antagonism known as allelopathy.

Agronomist Jerry D. Doll notes that dozens of allelopathic chemicals have been identified in the roots or foliage of weeds, crops, and forest species. These organic compounds include phenolic acids, long-chain fatty acids, terpenes, alkaloids, alcohols, and flavonoids. While many are growth inhibitors, some are growth stimulants.

"Allelopathy is a natural mechanism," says Doll. "The better we understand allelopathy in weeds, the better we can fight it. The more we learn about allelopathy in crops, the more effectively we can employ it to suppress weeds."

A main concern of crop scientists is identifying strongly allelopathic weeds. "In yellow nutsedge, for example, allelopathy is fairly clear-cut," he continues. "This weed grows from a tuber and is a serious pest, reducing crop yeilds in corn and soybeans."

Doll and graduate student Dirk C. Drost dried yellow nutsedge plants, ground them up, and soaked them in water to leach out allelopathic substances. The water extract was applied in various doses to both corn and soybean plants. Ground up residues of tubers and foliage were also mixed with soil in which corn and soybeans were subsequently planted.

"We found that the tubers of nutsedge were much more allelopathic than the foliage," says Doll. "Residues at seed depth inhibited germination, and residues in the active root zone of growing plants reduced root growth by as much as 40 per cent."

Doll notes that other perennial weeds also have strongly allelopathic roots or rhizomes. Quackgrass rhizomes, for instance, inhibit corn and wheat growth. Root exudates of giant foxtail inhibit corn, and velvet leaf is allelopathic against soybeans.

Many crop species also exhibit allelopathy, sometimes against one another. Wheat residue, for example, inhibits growth of corn and sugar beets as well as weeds.

Putting Allelopathy to Work

Allelopathy can be beneficial. "For example, it should be possible to raise a weed-suppressing winter cover-crop like wheat or grain sorghum, allow the crop develop allelopathic chemicals, then kill it in the spring and plant a crop of nonsensitive vegetables," says Doll. "Such an approach may not control all weeds, but it could help reduce weed growth."

Another way to enlist the forces of allelopathy is to selectively breed crop varieties with allelopathy toward weeds. Doll notes that Alan R. Putnam of Michigan State University has screened over 500 cultivars of cucumber. Among these, he found 26 that inhibited weed growth by 50 per cent. Similar work in New York with oats has turned up at least four varieties with strong allelopathy against wild mustard, a common-weed associate.

However, Doll notes that getting the greatest allelopathic benefit from a crop may require a change in cultiva-

tion methods. The allelopathic cucumbers, for example, must be planted earlier in spring and more densely than usual for greatest effect against weeds.

"We certainly don't expect farmers to abandon herbicides in favor of allelopathy," says Doll. "But it's common sense to use natural inhibitors whenever possible. It's one more way to tip the balance in favor of the crop."

Allelopathy Among Microbes

Plant pathologist John H. Andrews is investigating how allelopathy among the so-called "lower plants" can be used to combat crop diseases. His special interest is how the microbial community of the apple leaf wages war against apple scab fungus.

"All leaf surfaces are normally inhabited by a variety of yeasts, bacteria, filamentous fungi, and actinomycetes (a group of bacteria-like organisms)," says Andrews. "This microscopic community consumes sugars, amino acids, and other materials exuded by the leaf. Collectively, we call these organisms the leaf epiflora."

In Wisconsin apple orchards, the non-pathogenic epiflora share their leaf and leaf litter habitat with the apple scab, a fungus that creates grayish black lesions on the leaf.

"Current scab control measures usually consist of some 10 to 16 fungicide applications a year," says Andrews. "Not only is the scab building up resistance to certain of the fungicides, but the cost of the spray program is becoming prohibitive. On top of this, the Environmental Protection Agency is concerned about possible health hazards from certain fungicides and may restrict chemicals formerly available to growers. There are a lot of reasons for reducing fungicide use and searching for other options."

Andrews suggests that reduction of sprays may allow the leaf surface organisms to play a more active part in scab control. He has found that several members of the epiflora are strongly antagonistic to apple scab and can inhibit growth of the fungus. Some of the leaf microorganisms release toxic substances with an antibiotic effect on the apple scab. Others are simply better competitors than scab for the available food source, be it an agar culture or the nutrients on the leaf surface.

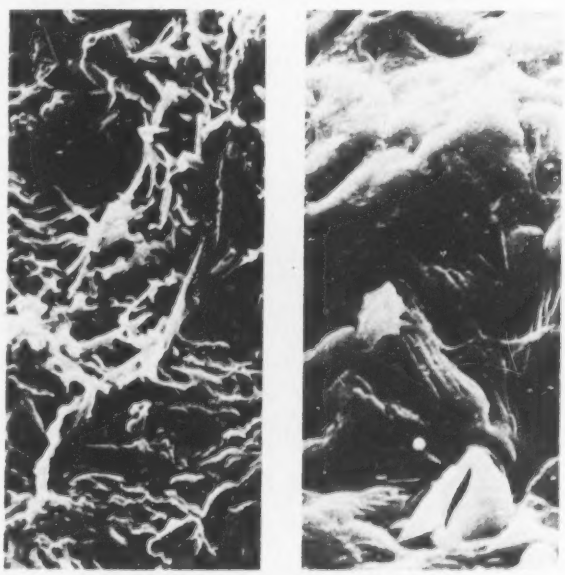
Andrews is testing the control potential of antagonistic epiflora in orchards. "We are spraying a suspension of leaf epiflora onto apple leaves and hoping these microbes will create an inhospitable environment for scab spores. We have had encouraging results from our preliminary field trials this summer," he says.

Sensitive to Fungicides

"Whatever we can do to encourage the growth of antagonistic epiflora should help control the scab," he adds. "But I certainly don't foresee orchardists doing without fungicides completely--and this may pose some problems to our biological control approach."

Many scab-antagonistic organisms are among those sensitive to fungicides. To counter this sensitivity, Andrews is trying to "train" certain antagonistic organisms to live with fungicides.

"The pathogen has developed resistance to fungicides, so why shouldn't the antagonists also become resistant," says Andrews. "It's mainly a matter of genetic selection. We culture the sensitive organisms on a medium containing a very low level of fungicide. Survivors from that culture are transferred to another medium containing more fungicide. Eventually we hope to produce a fungicide-resistant strain of bacteria, yeast or other microorganism that also retains its antagonism to scab. We might even be able to apply the fungicide and the tolerant organisms in the same spray," says Andrews.



Fungicides can dramatically reduce leaf epiflora populations. Under the electron microscope, untreated apple leaf (left) shows a dense cover of microorganisms. (right) A leaf treated with fungicide is almost devoid of epiflora.

Old Maps
(Cont'd from page 9)

Identifying and recording these minute changes in the shape or position of the watermark, then, is the key to dating the paper.

However, recording an accurate detailed image of a watermark presented almost insuperable difficulties until beta radiography was applied. This particular technique was first developed by botanists to study the internal structures of plant leaves.

To obtain a watermark image by beta radiography, a plastic sheet impregnated with carbon 14 is placed against the map. Next, x-ray film is pressed against the other side of the paper. As the beta rays emitted from the plastic pass more quickly through the less dense areas where the watermark wires touched the paper during manufacture, a precise negative image of the motif appears on the film.

Beta radiography allowed Woodward to catalogue the watermarks of a Venetian composite atlas containing 41 maps. Thirty of the maps carried a watermark in the form of an eight-spoked wheel. Close examination revealed that differences in the wheel watermarks showed that twin paper molds were used in manufacturing the paper.

"At this point it occurred to me to marshal another technique to compare and analyze the subtle differences between these watermarks," Woodward said.

With the assistance of engineer Frank Scarpace, Woodward placed the x-ray negative on a scanning densitometer, used frequently to analyze and interpret aerial photographs, and enhance film images.

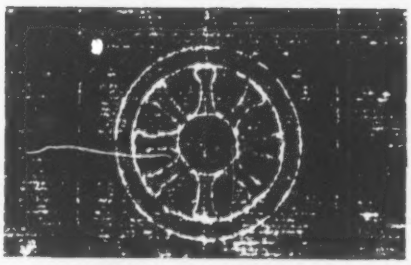
The device sends a tiny beam of light, as small as 50 micrometers, through the film negative and into a photoelectric receiver. The receiver, in turn, is linked to a computer which digitally registers changes in film density imperceptible to the human eye.

Armed with these methods, Woodward proceeded to arrive at a series of new conclusions concerning Italy's map-making industry.

First, discovering that an identifiable pair of watermarks dominates the maps of the Venetian atlas, Woodward inferred that maps were often printed to order in the sixteenth-century, and not always mass-produced, as had been previously thought.

"If the same watermark appears in an atlas containing a variety of different maps," Woodward explains, "this suggests that the atlas was custom made from the same batch of paper."

Due to the high cost of paper, it would have been unlikely, Woodward added, for a printer to keep preprinted maps in stock. If that were true, the same watermarks would appear in the same maps in other atlases. That, however, does not occur.



A watermark in the form of an eight-spoked wheel. Differences in the wheel watermarks showed that twin paper molds were used in manufacturing the paper.

Secondly, by identifying individual watermarks and changes in them due to wear, maps can be placed in a chronological sequence of manufacture. Woodward refers to this as the reconstruction of Italian map stratigraphy.

"We can almost pinpoint when, where and in what order maps were made during this important period, and also where they eventually ended up," Woodward says. Furthermore, since the images are recorded in the form of numbers—the coordinates of a tiny square and the film density within it—the watermarks can be statistically compared to bring out minute differences and even classified automatically to aid the sorting procedure. The comparison may be done by first adjusting the size images to account for paper shrinkage and then overlaying them statistically, whereupon the sewing knots used to attach the watermark to the mold will cluster in marks made from the same mold.

Commenting upon his experiences in dating watermarks, Woodward says that this specialized study expanded his vision as a geographer.

"I moved from interpreting watermarks, to the history of cartography, to a more general geographic study of the movement of maps throughout Italy and Europe," Woodward observes.

He also noted that beta radiography coupled with density scanning can be fruitfully applied to date other historical documents.

"Any document with a clear watermark, such as a piece of sheet music, a print, an archival document or a book could be dated using these techniques," concludes Woodward.

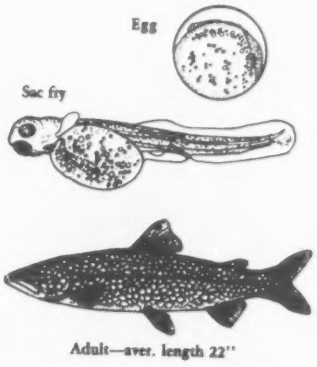
Restoring a Lost Resource
The Lake Trout Story

Marine scientists fight to reestablish natural populations of lake trout.

Linda Weimer
UW Sea Grant Institute

Lake trout were once the mainstay of the commercial fishery of the Upper Great Lakes region. But in the 1940s and 50s, the parasitic sea lamprey invaded the upper lakes and decimated native populations of trout in Lakes Michigan and Superior. The state and federal governments eventually brought the sea lamprey population under control and, in 1965, began stocking yearling lake trout in Lake Michigan in hopes of reestablishing the trout population and revitalizing the lake's fishery.

Sixteen years and 30 million young trout later, the fish have failed to reproduce naturally. Though they have fostered a multimillion dollar sport fishery, the lake trout that fill Lake Michigan sportsmen's creels were born and bred in a federal hatchery. Why the planted lake trout are not reproducing naturally is a question that university and government scientists are working hard to answer. Reestablishing natural populations of lake trout would save millions of dollars now spent in fish stocking programs.



Life stages of the lake trout **Salvelinus namaycush.**

Historic Spawning Sites

The lake trout's failure to reproduce may be linked to the sites where the fish had been planted. Until five or six years ago, truckloads of fish were dumped into the lake from locations along the shore—off piers and jettys, or near the mouths of rivers.

Ross Horrall and other scientists knew that, theoretically, the fish should return to those shore areas as adults to spawn, thanks to a biological phenomenon known as imprinting. But conditions in those areas of the lake were not suitable for lake trout spawning or for egg and fry survival.

So, with support from the UW Sea Grant Institute, Horrall, a fisheries biologist with the UW-Madison Marine Studies Center and Laboratory of Limnology, investigated where in the lake native trout had spawned in the years before the lamprey. Horrall and Catherine Coberly, then a specialist in the UW Marine Studies Center, developed a series of charts, delineating historic lake trout spawning grounds in both Lakes Michigan and Superior. Through interviews with 95 old-time commercial fishermen, Coberly and Horrall were able to pinpoint 35 sites in Lake Superior and more than 60 sites in Lake Michigan where lake trout had once spawned successfully.

The Reef Surveys

As a next step, Horrall's research team investigated some of these areas first-hand to find out why they had been so productive. Since 1978, project divers have surveyed 79 miles of underwater transects over historic spawning reefs in 13 areas of Lakes Michigan and Superior.

In these surveys, divers swim along the reefs, taking pictures and notes describing the lake bottom. They record the thickness, size and type of rock found, algae cover, silt deposition, and the presence of possible lake trout egg and fry predators. Oceanographer Phil Keillor of the UW Sea Grant Institute has installed meters to record lake currents and water temperatures at selected locations. All of these factors are important to successful lake trout reproduction.

These reef surveys, supported by the Wisconsin Department of Natural Resources, the Wisconsin Coastal Management Program and the Sea Grant Institute, have already helped improve the state's planting programs, notes Keillor.

From 1975 to 1980, for example, the DNR planted fish on Horseshoe Reef and Deathdoor Bluff Reef in Green Bay which were, historically, important lake trout spawning sites.

Lessons from the Salmon

Young hatchery-raised lake trout must be planted over areas where egg and fry survival is likely because like salmon, trout become imprinted to their surroundings early in life. They then return to those "remembered" places as adults to lay and fertilize eggs of their own.

Thanks to pioneering research by Arthur Hasler, UW-Madison Emeritus Professor of Zoology, and Ross Horrall, it is now well known that young salmon become imprinted to the odors of their home streams. Later in life, as spawning adults, the salmon recall that home stream odor and use that recollection to guide them back to reproduce in their natural areas.

Hasler and Horrall developed a method whereby young salmon could be "artificially" imprinted. The fish were exposed, while in the hatchery, to a synthetic chemical odor and were then planted in Lake Michigan. When the fish reached maturity, the chemical was dripped into the lake at points along the shore. The adult fish, remembering the odor, congregated at those points. Since its development, this technique has been used by several states to concentrate salmon in popular sport fishing areas.

Imprinted Lake Trout

"Lake trout also display a homing ability," says Horrall, "and we think they become imprinted in a way similar to the salmon. But we need to determine the critical imprinting period—at what age do the young trout form those lasting attachments to their home reef?"

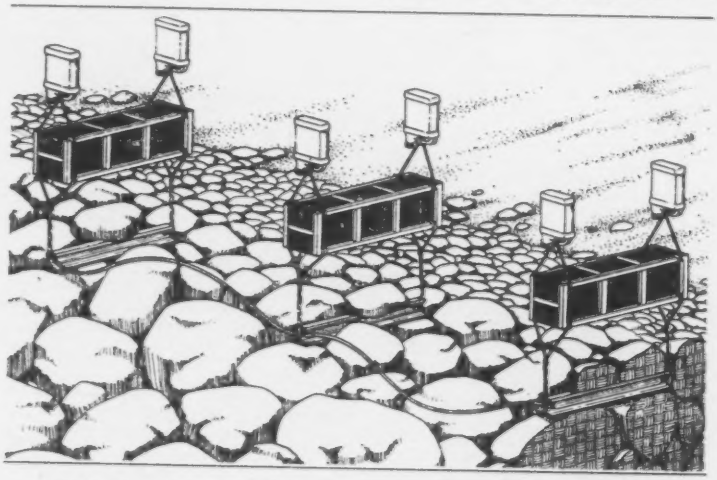
The scientists had hoped that 18-month-old trout yearlings planted on historic spawning reefs would become naturally imprinted to these sites. But evidence now suggests that the fish may already be too old, when planted, to strongly imprint to these places.

"I think the critical period may just be after hatching," says Horrall. "No one has looked at lake trout but scientists have shown that the olfactory system is already functioning in a sockeye salmon just after it hatches."

Given the success of the artificial imprinting work with salmon, Horrall is trying a similar experiment with lake trout.

Prior to the 1980 trout plant in the Clay Banks reef area, Horrall travelled to the Jordan River National Fish Hatchery in Michigan. There, he exposed about 128,000 young trout to a chemical odor in an attempt to imprint them artificially. Soon after that, those fish and about 172,000 others that had not been chemically imprinted were planted in the Clay Banks area.

In four or five years, when these fish are mature, Horrall intends to introduce the imprinting chemical to the waters



A diver's sketch shows the arrangement of the "astroturf incubators," anchored over what was once a productive lake trout spawning area in Lake Superior. Thousands of lake trout eggs, protectively nestled between layers of "plastic" grass, have been planted in the lakes by the Wisconsin Department of Natural Resources.

around that planting site and see if it will attract the imprinted trout.

The Largest Lake Trout Plant

The 1980 Clay Banks stocking effort was the largest Wisconsin lake trout plant ever made in one area. The state DNR put roughly a third of its supply of yearlings in that single site in Lake Michigan.

Many experts have contended that there are not enough lake trout in any one area of Lake Michigan to reestablish the population and that such massive plants are needed to ensure that there will be enough spawners in an area to produce a viable number of eggs and fry.

"If the lake trout plants are spread too thin, there won't be the critical mass of fish needed to get subsantial reproduction in any one place," observes Horrall.

An Experimental Hatchery

The UW lake trout research group is also trying another approach to imprinting and planting a "critical mass" of lake trout.

In the city of Green Bay's water pumping station on the shores of Lake Michigan, Phil Keillor engineered and helped install a small, experimental trout hatchery. There, the scientists raised almost a million lake-trout eggs, using water taken from 50 feet down in Lake Michigan. The water temperatures in the hatchery, therefore, closely resembled those in which a native lake trout would be reared.

In May, after the eggs had hatched, the research team took the sac fry to a spawning site in Green Bay located during the earlier reef surveys. There, divers seeded the reef with the tiny fry. Of the million eggs raised in the experimental hatchery, over half survived to be planted on the reef; of those, 5-10 per cent may ultimately survive to adulthood.

"We might have 25-50,000 fish come back to spawn," Horrall notes.

"Since sac fry can be imprinted to the stocking site much more precisely than yearling fish, we stand a much better chance of getting the fish to spawn where we want them to."

At the same time, Horrall, Keillor and the UW divers have been assisting the Wisconsin DNR with a lake trout egg planting project. Last fall, the agency planted more than 200,000 eggs, nestled in protective astroturf sandwiches, over reefs in Lakes Michigan and Superior. During the winter, 80 to 90 per cent of the eggs successfully hatched out and the biologists hope the sac fry became imprinted to the reefs.

Egg Plants and Pheromones

One advantage to planting eggs and fry in the lake, is that adult trout may be attracted by the scent of young trout or spawning debris like dead eggs or fish mucus, says Horrall.

Recent evidence suggests these materials may yield pheromones, chemical substances produced by an animal that evoke behavioral responses in other members of the same species. Lake trout may imprint to such pheromones and these may trigger or stimulate spawning in the adult fish.

A UW diver enters Lake Michigan to survey an historic lake trout spawning area.

Horrall is also excited about the genetic experiments that the small, experimental hatchery is making possible. He has reared eggs from several different strains of trout and has recorded their developmental differences during the winter.

Next year, if the hatchery continues, Horrall wants to cross different strains of lake trout in hopes of selecting out those best able to survive conditions in the lake to reproduce there. He believes genetic considerations play a crucial role in the whole reproductive process. He notes that most of the lake trout now being planted in Lake Michigan are from a Lake Superior strain of fish.

"There's a chance that the fish being stocked are so adapted to hatchery conditions that their offspring cannot survive under natural conditions in the lake. For example, natural selection may be favoring fish that do well, as eggs, in the warmer water of the fish hatcheries as opposed to the colder waters which occur in the lake."

The "Green Lake" Strain

Years ago, before the lamprey invasion, there were actually five or six distinguishable strains of lake trout in Lake Michigan. Remnants of one, the "Green Lake" strain, were discovered in a hatchery just as plans were afoot to dispose of the fish.

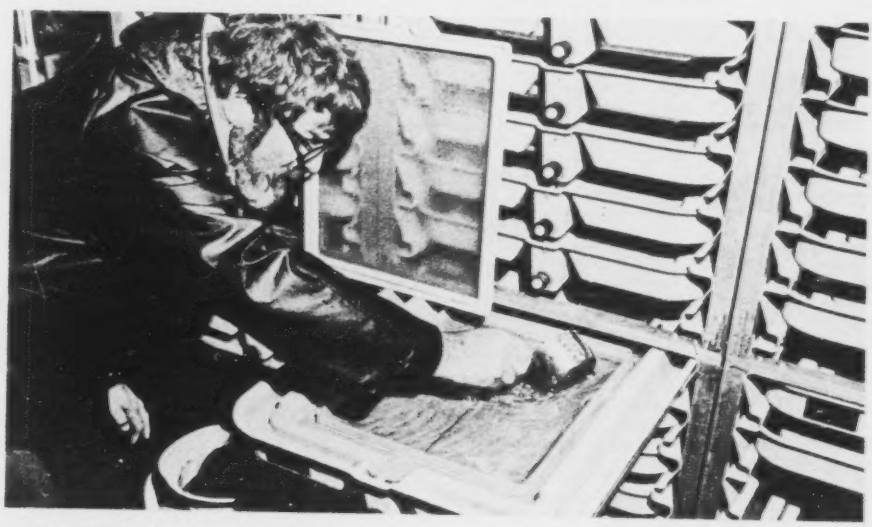
Horrall alerted the Wisconsin DNR and the Great Lakes Fishery Commission and the agencies agreed to save some to develop a new brood stock. In 1976, some 277,000 of these trout were planted on the Sheboygan Reef, a deep reef complex in south central Lake Michigan that was the Green Lake strain's ancestral home.

This year, the DNR established a refuge on this reef to protect these trout from fishing pressures. Monitoring efforts indicate that the Green Lake strain is doing well. With the sexual maturation of these fish, the scientists hope to find evidence of natural reproduction.

"At the moment, this Sheboygan Reef population offers the best chance in Lake Michigan for a lake trout stock to become self-sustaining," says Horrall.

Planting the Green Lake strain on Sheboygan Reef; sprinkling historic spawning sites with tiny sac fry; using chemicals to imprint eggs, fry and yearlings; making massive fish plants in a single area; planting eggs over the reefs; coming up with new genetic strains of lake trout better suited for reproducing in the lake environment—which, if any, of these gambits will succeed in restoring native lake trout to Lakes Michigan and Superior remains to be seen.

If it can be done, the state and federal governments could save millions of dollars in fish stocking and hatchery costs, sport fishermen could be assured of the continued presence of the popular lake trout, and commercial fishermen could; perhaps, harvest more of this species. But most important, the work being done by the UW-Madison research team, in concert with the Wisconsin DNR, may bring back a natural resource, thought to have been lost forever.



Ross Horrall works with tiny lake trout eggs that fill the UW's experimental hatchery at the Green Bay water pumping station on the shore of Lake Michigan.

UW-MADISON

Endangered Species: Setting Priorities on Which Ones to Save

"We're losing species before we have any idea of their value."

Ann Beckel

The number of plant and animal species threatened with extinction is increasing at an ever-accelerating rate, as the human population expands and demands for land, energy, timber, and other resources grow.

"The revised Red Data Book for birds, which lists endangered species throughout the world, is twice as large as it was in 1968," says wildlife ecologist Stanley A. Temple of the University of Wisconsin-Madison.

"Species become endangered through the direct and indirect effects of humans—primarily overkill, habitat loss or deterioration, and, to a lesser extent, pollution."

Species threatened with extinction present two basic challenges to conservationists, explains Temple, who has conducted extensive research on endangered species, such as California condors, whooping cranes, peregrine falcons, Mauritius kestrels, and Hawaiian birds.

The first challenge is to keep species from becoming endangered, the second is to restore endangered species to a non-endangered status.

"Scientists can play only a small role in keeping species from becoming endangered. That's primarily a political and economic challenge to society," says Temple. "But as repairmen of ecosystems, scientists can play a major role in restoring species."

Setting Priorities

The number of threatened species is so large and current conservation techniques so labor intensive that it is impossible to save all endangered plants and animals.

"We'll soon be facing very difficult questions about which species to save and which ones to allow to go extinct," Temple contends.

"Conservation decisions traditionally have been based on emotional appeal rather than on scientific criteria. The big, beautiful, dramatic species get the help."

Basing decisions on scientific criteria, however, is fraught with controversy. Conservationists argue among themselves whether efforts should be directed at species closest to extinction or toward plants and animals with important roles in biological communities. Or should the most time, money, and labor be spent on species that are taxonomically unique, ones that are endangered throughout their entire range, or species that are most useful to humans?

There are major drawbacks to each approach. If conservation efforts are concentrated on plants and animals whose populations are smallest, for example, resources may be wasted on species that are already doomed, says Temple.

The population of California condors, for example, has been in steady decline since the 1930's, and Temple estimates that there are no more than 30 left.

"The condor is in the eleventh hour. It may be a species that's already over the brink."

In a world where social, political, and environmental problems abound, why should people care if condors, snail darters, mountain gorillas, or furbished lousewort cease to exist?

"Everyone has his/her own reasons for wanting to save species. To many people, human-caused extinction is a moral and philosophical issue," Temple explains.

"But there are other reasons for wanting to save endangered species. Most of these species are not well-studied, so their potential uses to humans are unknown."

Many drugs, for example, are derived from plants and animals. It is estimated that about one-third of pharmaceutical drugs come from tropical plants alone, and yet only a small proportion of species have been investigated for medicinal properties. An even smaller proportion have been tested for industrial and agricultural uses.

"We're losing species before we have any idea of their value," says Temple. "Species extinction also simplifies biological communities, which in some cases, can lead to community instability.

"As a biologist, I also have selfish reasons for wanting to save species. Extinction means losing an opportunity for studying the diversity of life. Everything about life can't be learned from laboratory rats and fruit flies."

Rescue a Difficult Challenge

Rescuing a species from imminent extinction is a difficult challenge to meet.

"By definition the population of an endangered species has dwindled to precariously low numbers. The first step has to be increasing numbers rapidly by whatever means possible," Temple explains.

Very little is known about the biology of most endangered species, however, and different species require different conservation strategies. Scientists and conservationists are left with an emergency room situation—they need to act quickly, but are not sure what should be done.

Strategies tried in the past include prohibiting the killing or collecting of endangered species, controlling competitors and predators, and breeding animals in captivity and reintroducing them into the wild. These techniques have proved successful for many plume-bearing birds, for example, which were decimated for the sake of fashion in the early 1900's, and for

99-177 O - 82 - 15

Endangered Species: An Economic Perspective

How does a society determine if the costs of saving a species are too large?

Ann Beckel

Extinction of plants and animals is an economic issue according to natural resources economist Richard C. Bishop of the University of Wisconsin-Madison.

"Vociferous proponents of short-run economic gains often carry the stage in controversies involving development versus conservation," says Bishop.

"A careful analysis of long-run economic gains, however, often reveals that the arguments of the side advocating extinction just don't hold up. It's not automatically economical to let a species go extinct."

Bishop does not advocate saving species at any cost, but contends that the economic approach is to keep species around unless the costs are unacceptably large.

"Even a society that places a high priority on stewardship of nature could quite rationally choose to extinguish a species because the costs of saving it are simply too large," says Bishop.

The biosphere can be thought of as a vast reservoir of potential resources, Bishop argues. Because species extinction is irreversible, it represents the permanent commitment of a potential resource, a permanent narrowing of the reservoir.

According to Bishop, natural resources do not just exist—they become. "Something in the natural environment becomes a resource when people recognize it has value to them," explains Bishop. "Whether something becomes a resource in the future depends on all sorts of social and technological changes. Consequently, the 'becoming process' is highly uncertain.

"Far too little is known about the attributes of plants and animals and about future social and economic circumstances to say which species can be safely discarded and which must be maintained."

But how does a society determine if the costs of saving a species from extinction are too large?

"In most cases that have been analyzed, the costs of maintaining endangered species are not severe and in some cases, the costs are negligible," Bishop says. "The cost of protecting the California Condor's habitat, for example, is about $3.2 million per year or about one per cent of what Americans spend for cat litter each year."

Bishop maintains that part of the economist's job is to help decision-makers and society realize that potential extinction is an economic issue, and secondly to determine what the costs and benefits of conservation are. Society must decide if the costs are acceptable.

A major difficulty is that the costs of maintaining endangered species fall on the present generation while the benefits may be realized only by future generations. So at first glance, the costs may seem too great to the present generation, especially in underdeveloped or developing countries.

The survival of mountain gorillas, for example, is severely threatened by human encroachment on their habitat, including two adjacent parks in Rwanda and Zaire. Rwanda is the most densely populated nation in Africa and the population is growing at an explosive rate. Some Rwandans advocate converting a large portion of the park to agriculture—a move that would gravely threaten the already precarious future of the park's gorillas.

"How can you ask people who are living on the margin of existence to give up land for gorillas?" says Bishop. "A closer look at the situation, however, reveals that the land's suitability for agriculture is highly questionable. Even if it is farmable, the additional land will accomodate only 25 per cent of one year's population growth.

"Moreover, the mountain gorillas could be a major tourist attraction and provide a much-needed source of revenue for Rwandans."

Despite indications that the costs of maintaining most species would not be great and that in many cases, benefits may easily exceed costs, endangered species lists are growing more rapidly than ever.

"Species extinction is a global problem. Plants and animals are going extinct at such a fast rate that species are lost before we can even come to grips with the problem."

---

sea otters, which were brought to the brink of extinction by demand for furs. The population of peregrine falcons has increased as a result of a captive breeding and reintroduction program that Temple directed before coming to Wisconsin.

Other conservation strategies commonly employed involve protecting the endangered species' habitat, or even improving it by adding nest sites or providing supplemental food, for example, or by reducing contaminants such as DDT, PCB's, and other toxic chemicals.

"All these techniques have the potential for preventing imminent extinction, but they rarely improve the condition that got the species into trouble in the first place. They are short-term, crisis-management techniques that can save a species, but can't secure its future," says Temple.

"The central problem is too many people affecting too much of the earth. The ultimate solution has to be to curb population growth. If the human population continues to grow, endangered species lists are certain to grow longer and more species will become extinct."

A Cost–Benefit Analysis of Road Salting

A policy of salt reduction trades off the corrosive, salt, for the abrasive, sand.

Ed Daub
NSF Public Service Resident

Professor Ed Daub recently served as NSF public service science resident at the Center for Public Representation. His role was to offer technical background to policy issues in transportation. The following article on a problem that arises each winter in the northern states appeared first in the newsletter of the Center for Public Representation, "The Public Eye," and is reprinted here with permission of that publication.

A query has come from Keith McCaffery of Rhinelander as to whether any cost/benefit analyses have been made of road salting. "I'd prefer," he said, "to drive less and slower with some increased risk of a fender-bender than 'safer' with a guarantee my vehicle will be destroyed by corrodium crudate."

Keith's sentiments express the point of view found in the report done for the EPA by Abt Associates in the mid-70's. It estimated that the total annual cost to owners of motor vehicles due to corrosion from road salt amounts to more than $2 billion, and Donald Murray who co-authored the Abt report has recommended that "there should be greater emphasis on training drivers in the skills of snow and ice driving and less emphasis on the concept of guaranteed June travel in January." Murray further noted that some studies suggest that improvements in highway condition also bring increased speeds and thus cancel the gains made in accident prevention. Far better then, perhaps, to have everybody drive with greater care and thus cope with winter road conditions.

Murray's opinions found no favor with Robert Brenner of the Institute for Safety Analysis who jointly authored a rebuttal to the Abt report, "Benefits and Costs in the Use of Salt to De-Ice Highways," a study funded by the Salt Institute. Commenting on Murray's paper in the*Transportation Research Record* in 1977, Brenner voiced the views that govern the practices of highway safety engineers: "Murray invokes the time-worn argument of driver behavior. We must recognize that, in the highway field, we design to be forgiving of driver error. We do not pass off hazardous conditions by saying the driver should learn how to cope with them. We do not design roads with poor sight distance and leave it to the driver to adjust to the danger."

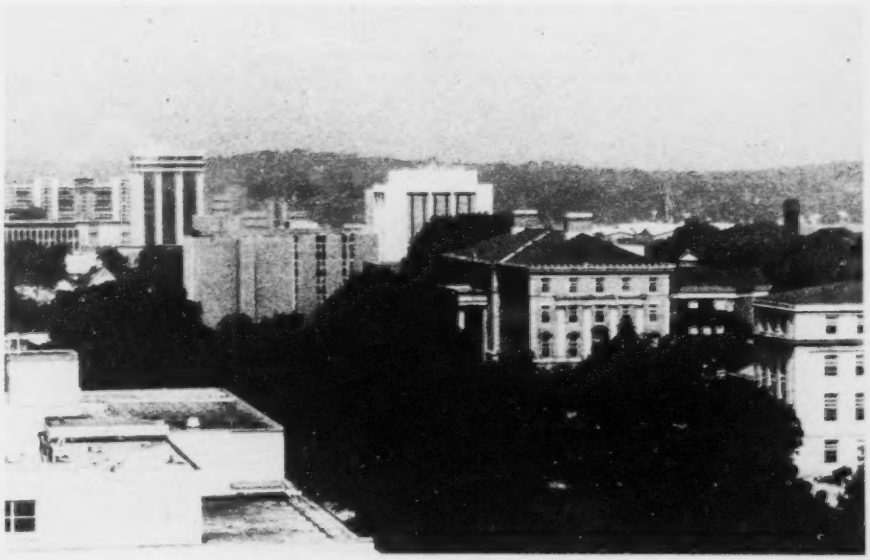
Thus, the authors of the two reports offer contrasts in their priorities for how to attain highway safety. They also differ in the emphasis given to costs on the one hand and to benefits on the other.

The Abt report focused solely on the economic costs of the environmental impact of highway deicing with an estimate of $3 billion. In addition to the costs due to vehicle corrosion, for example, it estimated the health hazard costs due to increasing the sodium content in ground water, measured by the probable annual cost of digging new wells or by the purchase of sodium free water by persons suffering from hypertension.

The study by the Institute for Safety Analysis, in contrast, argued the health benefits that highway deicing brings, namely, the benefits it provides by making emergency medical services available to persons injured in traffic accidents and to those who suffer heart attacks. In the case of traffic accidents, for example, an Australian study of traffic fatalities showed, through post-mortem examinations, that 26 per cent of the fatally injured had possessed the potential to survive. Moreover, in another study of emergency treatment cases in the United States, it was found that the chances of surviving a serious trauma drop off rapidly as the delay in treatment increases beyond 20 minutes. If the delay reaches 3 hours or more, the survival chance drops to only 5 to 10 per cent. The report estimated, therefore, that delays of three hours in emergency services, due to ice and snow, could mean a difference of 472 deaths per year in the United States because approximately 2000 traffic fatalities occur every year under those conditions.

An Expression of appreciation by the University of Wisconsin-Madison Graduate School on the occasion of the 50th anniversary of the Wisconsin Alumni Research Foundation

1925-1975



The Wisconsin Alumni Research Foundation: A Story of Dedication

One of the amazing aspects of the Wisconsin Alumni Research Foundation story has been the intensive involvement of UW alumni in WARF activities. They have been a part of the program from the beginning. Alumni provided the initial wherewithal to facilitate the organization of WARF. Since 1925, they have served as trustees of the Foundation.

Looking over the list of past and present WARF trustees, I am impressed by the quality of persons who have been selected. These individuals have all had distinguished careers in their own professions and they have demonstrated their uncommon loyalty to the University of Wisconsin through long service to WARF.

The skill and devotion the trustees have demonstrated during the first half century of WARF's history has produced one of the remarkable success stories of alumni commitment to University activities. The record of their achievements can be witnessed in the continuing high level of grants that are given to the University each year to support a number of activities which are essential to sustaining the intellectual well-being of the campus.

We are proud, on this anniversary, to pay tribute to WARF and to the excellent leadership provided by the trustees and staff during the first fifty years of development. The University is constantly aware of the extra dimension of quality that the Wisconsin Alumni Research Foundation has given to our teaching, research, and service programs.

Edwin Young

WARF:
50 years

...And a Dream Fulfilled

Few organizations have survived the last half century of change—of depression, of war, of rapid growth and retrenchment—and continued to carry out their intended roles as consistently and as effectively as has the Wisconsin Alumni Research Foundation.

This vigorous survival is ample testimony to the foresight of those who created the Foundation. For more than half of these fifty years I have observed their dreams being realized as bold research ideas were pursued, able students educated, needed facilities built, new ideas brought to the University and well deserved recognition bestowed on dedicated researchers.

This short booklet is an overview of some of the many exciting phases of WARF's first half century. I welcome the opportunity this anniversary gives us to pause and recall the happy past as two good friends, WARF and the UW, look to the future with the enthusiasm and confidence made possible by the foresight of WARF's founders and all those who have shared their dream.

Robert M Bock

The Germination of an Idea

Harry Steenbock, 1960

"A powerful example that lived through the years."
Professor Harry Steenbock in his laboratory

Late in the fall of 1923, Harry Steenbock, a young biochemist at the University of Wisconsin, made a startling discovery. He found that he could prevent—or even reverse—the symptoms of rickets in rats by feeding them a mixture of millet seed and casein that had been exposed to sunlight or other source of ultraviolet light. Further experiments showed that the irradiation treatment induced synthesis in the ration, and in many other foods, of the "fat soluble vitamine D" which had just been discovered by Elmer V. McCollum, a former colleague of Steenbock at Wisconsin.

In 1923, both vitamin D and sunshine were known to prevent or cure rickets, a crippling, bone-softening disease which had become widespread among children in the century since the industrial revolution. But the relation between the two curatives was a mystery. By linking them, Steenbock had shown how to trap some of the magic of sunlight—its power to form one of nature's rarest vitamins—in a box of cereal or a bottle of milk.

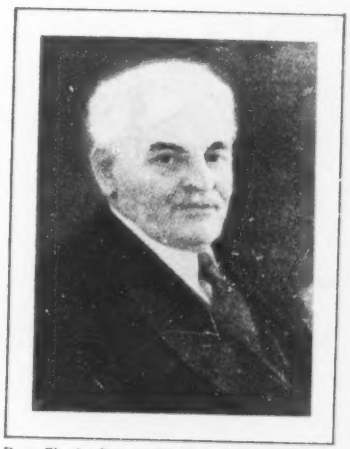
Although many other vitamin researchers did not immediately recognize this, Steenbock saw that the results of the experiments he was completing just a few days before Christmas held enormous promise for public health.

In 1923, however, the route to widespread fulfillment of this promise was far from clear, as Steenbock himself had good reason to know. There was evidence in recent University history that the easy way of introducing an idea to the public—simply publishing it and abandoning it to commercial interests—was not always the best way. Three decades earlier, when Professor Stephen Babcock had released his

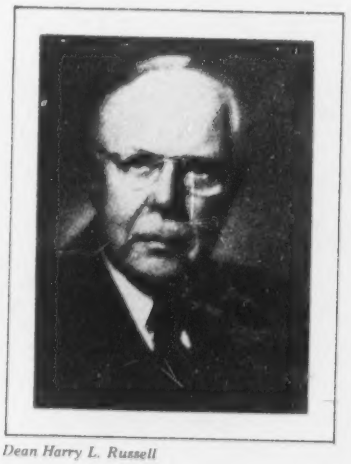
"You may well ask: then why did I do as I did? The answer is: it is all an experiment." Steenbock

famous milk butterfat test in this way, its development had been uneven and cut-rate models of his machine had even proven dangerous to those using them. So it seemed that, in some cases at least, a patent on a new idea, giving the discoverer some control over its commercial development, seemed called for.

But patenting the irradiation process would be a complicated affair, one which Steenbock had no desire to undertake on his own. Taking out the patent would be expensive; managing it would take up time he wanted to spend in his laboratory. And, if successful, the patent would yield royalties which, Steenbock stoutly believed, ought to return to the University at which the idea behind it had been conceived.



Dean Charles Sumner Slichter



Dean Harry L. Russell

Just a few years earlier he had found the Regents cold to his suggestion that they take out and manage for the benefit of the University a patent on a process he had developed for the isolation of vitamin A. Clearly, if his latest discovery were to yield its full benefit to society and to the University, it would have to be matched by yet another idea. And it was in Steenbock's search for this idea that the Wisconsin Alumni Research Foundation came into being.

Inklings of a plan came from Chicago where William Hoskins, a consulting chemist, and Russell Wiles, a patent attorney, had put together a plan for a patent-managing foundation which would provide money to a university but which had the novel feature of carefully separating its management from the university's. Steenbock learned of Hoskins' and Wiles' plan early in 1924. He liked it and discussed it with Harry L. Russell, then dean of the School of Agriculture, who shared his enthusiasm for it and carried it to the Regents, hoping for money with which to fund the needed patent application. The Regents, however, saw the scheme as a speculative venture, well outside their authority as managers of public funds. They turned it down and for nearly a year the project was stalled, a fertile field, plowed and seeded, waiting for rain.

Then, in the spring of 1925, just before the deadline for filing for patents on the irradiation process, the needed help came. Talk of Steenbock's and Russell's efforts had come to Graduate School Dean Charles Sumner Slichter, and Slichter invited Steenbock to discuss his idea with him over lunch at the Madison Club.

What Slichter learned at that meeting amazed him. Here was a member of his faculty who had been struggling for more than a year to make a present to the University of a discovery that not only held the promise of relieving widespread human suffering but which clearly had enormous market value. Already the Quaker Oats Company had offered Steenbock $900,000 for exclusive rights to a patent on his irradiation process. But so far those at the University who controlled the money which would be needed to take out a patent had given him no encouragement at all.

Slichter left that lunch a convinced man.

"I'll go to New York right away," Steenbock, thirty-five years later, recalled him as saying, "and I'll come back with plenty of funds to set up your foundation."

ARTICLES OF ASSOCIATION

UNITED STATES OF AMERICA,

THE STATE OF WISCONSIN,

DEPARTMENT OF STATE.

To All to Whom These Presents Shall Come:

I, Fred R. Zimmerman, Secretary of State of the State of Wisconsin, DO HEREBY CERTIFY that on the fourteenth day of November A. D. 1925, there was filed in the Department of State an instrument in writing, purporting to be Articles of Association, with a view of forming a corporation to be known as

WISCONSIN ALUMNI RESEARCH FOUNDATION

Within a few days, Dean Slichter had left on the mission he had promised Steenbock he would undertake. Stopping in Chicago and New York, he contacted key University of Wisconsin alumni, urging them to lend funds toward the formation of a foundation which would manage patents on the irradiation process for the benefit of research at the University. He returned with pledges for $10,000—to which he himself added $2,000—for further research and a patent application. He also had promises from several alumni to accept posts as trustees of the foundation once it was set up.

Money to set up the foundation itself was not long in coming. Shortly after his eastern trip, Slichter invited a group of alumni to his summer home on the north shore of Lake Mendota to discuss the developing foundation idea. The meeting at "Slichter's shack" was recalled 34 years later by Chicago Attorney Charles L. Bryon in a letter to Emeritus President E. B. Fred:

> "Those present, in addition to Dean Slichter, Harry Steenbock, and David Barney*, were Max Mason, George I. Haight, Judge Evan A. Evans, Justice Burr Jones, Harry Butler, Bill Keyes, (sic) Lou Hanks, Tim Brown and myself. After a most delicious fried chicken dinner and some wonderful flat-shaped Drury Lane cigars Dean Slichter, in giving his promotional talk on the Steenbock inventions and their great possibilities, electrified us into action. Enthusiasm reigned supreme, and the organization . . . was effectively started. Near the end of the meeting Dean Slichter said, 'We owe $900 and we must clear up that situation immediately.' He suggested that each of the last nine named men give $100. This was done. You know the rest of the story."

Early in May, Slichter and Russell again went before the Regents—this time with a proposal that would cost the University nothing at all and that clearly stood a chance of yielding considerable support to its growing research program. The Regents approved the plan in this form and the work of drawing up a charter got underway.

The charter was the work of five men: Steenbock, Slichter and Russell plus Alumni George Haight, a leading patent attorney from Chicago, and Madison Attorney Harry Butler. The document, in its finished form, reflected the ideas of all these men and drew on the experience of foundations that had been set up at Columbia University and the University of California, and especially on the plan proposed by Hoskins and Wiles. One feature it borrowed from this plan which was to prove crucial to the success of the foundation was the provision that its management be wholly independent of the University administration. The foundation was to be managed for the benefit of the University, but wholly by outside friends of the University. Foundations having some connection with an educational institution have since been set up all over the country and at all types of institutions, but WARF was the first to be formed as an agency independent of faculty or regent control and having no other endowment than a patent.

The charter was granted on November 14, 1925. Under it, the Foundation would have no capital stock and would pay its members no dividends. Its only business would be to aid research at the University through grants made from income accruing from patent management, investments and gifts. Its trustees were to be five Wisconsin alumni, a number which has since risen to 17.

**Barney joined the foundation in 1932 and was not, in fact, at this meeting.*

The First Trustees

From its inception, the dedication of the trustees of the Foundation to the growing task of managing the WARF patents and investment portfolio has been a key to its success. The first trustees, selected by the founders from Wisconsin alumni prominent in business and law, established a tradition which continues to the present day. In addition to Haight, who became the Foundation's first president, they were: Madison investor Thomas E. Brittingham, Jr., Madison Attorney Timothy Brown, Madison Bank President Lucien Hanks and New York Attorney William S. Kies.

Between them Brittingham, Haight and Brown were to spend more than 600 days guiding the Foundation through its first quarter century.

Thomas E. Brittingham '21

Lucien M. Hanks '89

George I. Haight '99

William S. Kies '99

Timothy Brown '11

Growth, Through Patents

Still on WARF's list of active patents is a device, shown here with its inventor, Pharmacy Professor Dale E. Wurster, for coating pills and tablets in air suspension. Since its invention in 1958, Wurster's machine has also been used to apply germination-controlling coatings to seeds and bait coatings to another WARF item, the rodenticide Warfarin.

On February 18, 1927, Professor Steenbock signed over to the Wisconsin Alumni Research Foundation his rights to the vitamin D irradiation process. In return he received ten dollars. "Probably," an article in *Reader's Digest* was to declare 13 years later, "ten dollars never bought so much before in history."

What it bought was a patent that made possible the orderly and responsible introduction of the irradiation process to the marketplace and that, at the same time, brought in handsome royalties.

The value of Steenbock's irradiation process to society has been incalculable. It has been estimated that as many as half the children in America had some degree of vitamin D deficiency at the time Steenbock made his discovery. In some of these cases the deficiencies resulted in permanent crippling and disfiguration. Available sources of vitamin D, notably the infamous cod liver oil, were unpopular and expensive; Steenbock's inexpensive way of introducing the vitamin into everyday foods like bread and milk soon made it readily available to all.

Applications for licenses to use the process flooded WARF's offices. The applicants included manufacturers of products ranging from chewing gum to cosmetics. The licenses, however, went to manufacturers of more substantial food items. The first licensee was the Quaker Oats Company, which had been negotiating with Steenbock since shortly after he made his discovery for rights to use irradiation to enrich its rolled oats. Soon several pharmaceutical firms were licensed to produce and market a vitamin D concentrate called Viosterol.

Later, WARF began licensing milk producers, and milk, its high calcium, phosphorous and fat content making it an ideal carrier of vitamin D, became the standard source of the vitamin which it still is today. In 1933, Richard Byrd carried evaporated irradiated milk on his Antarctic expedition.

By the time the Steenbock patent expired in 1945, it had produced about $8 million in net royalties, and rickets had been eliminated as a major health problem.

The campus currently yields new patent ideas at the rate of about 60 each year, or more than one each week. Since 1925, members of the faculty have approached the Foundation with more than 1,500 suggestions for patentable ideas which have arisen from their research—in many cases research that has itself been supported by money from the Foundation. Of

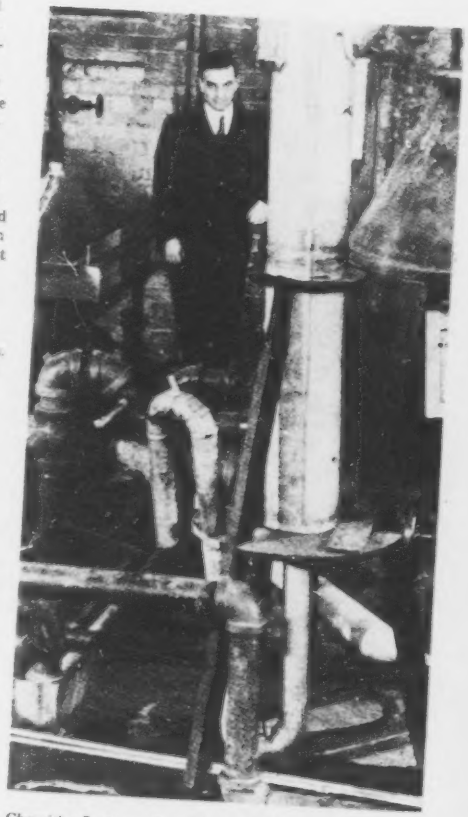
these, about 250 have actually been awarded patents and 42 have yielded a profit in royalties. Many of them have significantly advanced scientific knowledge as well as contributed to the betterment of the human lot. Notable among these on both counts have been the patents on the discovery by Biochemistry Professor Karl Paul Link, of the blood anticoagulants dicumarol and Warfarin. These compounds, relatives of coumarin, which Link isolated from spoiled sweet clover hay, have given physicians a new measure of control over clotting of the blood in surgery and in the treatment of certain diseases of the circulatory system. Warfarin, named from the Foundation's initials, is now used all over the world as a rodenticide. Together, the patents on Link's discoveries have been one of the Foundation's largest producers of net royalties.

Many other discoveries assigned to the Foundation have been useful in medicine. These include Biochemist E. B. Hart's preparation of copper and iron used to relieve anemia, his method for stabilizing iodine in table salt, and a solution devised by Physicians Manucher Javid and Paul Settlage which relieves pressure on the brain in patients with brain tumors or head injuries.

Other inventions have come to WARF from the departments of chemistry, pharmacy, soil science, bacteriology, food science, engineering departments and many others.

In all cases these have been assigned to the Foundation voluntarily, with 85 per cent of the net royalties going to the Foundation and 15 per cent being shared by the inventors.

Altogether, of WARF's 42 winners, three have produced more than $1 million each in royalties; nine have produced between $100,000 and $1 million and 14 have produced between ten and one hundred thousand dollars.



Chemistry Professor Farrington Daniels, shown here amidst the piping of one of the early models of his nitrogen fixation furnace, assigned several patents to WARF, including an early solar engine and applications of the phenomenon of thermoluminescence.

A Vision in a Bucket of Blood: The Discovery of Warfarin

One snowy morning in February, 1933, Ed Carlson, a farmer from Deer Park, Wisconsin, came into Karl Paul Link's laboratory carrying a milk can full of blood that refused to coagulate. Outside he had a small heap of spoiled sweet clover hay and a dead heifer freezing in the back of his truck.

Studies on the factor in spoiled sweet clover hay that killed cattle by hemorrhaging were already well underway on campus in 1933. R. A. Brink and W. K. Smith in Genetics had been trying to breed a strain of clover free of its prescursor for several years, and efforts to isolate it were underway in Link's laboratory. But Link is an emotional man and, for him, the story of Warfarin really began with Ed Carlson's visit.

The first paper describing the concentration of the hemorrhagic factor appeared in the October, 1940, issue of the Journal of Biological Chemistry. "It was," Link recalls, "a modest paper. My rule is, never overstate your case in print. It's better to understate it and let the facts speak for themselves."

In successive papers the facts did so most eloquently. In 1941, Link and Harold Campbell reported the isolation of dicumarol, the first of the oral anticoagulants now widely used in surgery and treatment of circulatory disorders. At the same time, Link was rapidly becoming convinced that the anticoagulants being isolated and synthesized in his laboratory might also be useful as rodenticides.

"From the beginning," he recalls, "I had an intuitive feeling that this might be a good thing. A pretty bad thing for rats; a good thing for humans. But the idea didn't come overnight. It came into my head and the heads of everyone in the lab over a period of years."

Again, the accumulating facts spoke for themselves, and in 1948 Link came to WARF Director Ward Ross with the suggestion that the Foundation patent, as a rodenticide, the coumarin derivative he later named Warfarin.

Why did Link turn over his patents to the Foundation?

"Well, they couldn't have been developed without the Foundation," he says. "I couldn't have done it myself and I never thought of trying.

"And I'm a loyal Wisconsin man. After all, I went to school here. I came as a freshman in 1917 and I got all my degrees here.

"In a broad sense, I wanted to do something for the University."

Karl Paul Link, discoverer of Warfarin, in his laboratory about 1950

And Investments

While patent royalties provided the seed money for WARF, continued growth has depended largely on investment of assets by the Foundation's trustees. Under their skillful and devoted stewardship, the Foundation's original gift fund of $900 has grown to nearly $100 million.

Founder George Haight became the first president of the WARF trustees in 1926 and served until his death in 1955. Brittingham succeeded him and was president until his death in 1960. Brittingham's successors, shown on this page, have been limited by new bylaws to four one-year terms.

Donald C. Slichter, 1960-64

William R. Kellett, 1964-68

Walter A. Frautschi, 1968-72

Haakon I. Romnes, 1972-73

Stanley L. Rewey, 1974-

WARF's Administrative Heads

"We have wanted to build a great Foundation in order to help build a great University"

Edwin Rosten, 1975

By 1929, the trustees, realizing that, unless they got help, the increasingly complex job of managing Foundation affairs would soon force them to give up their own professional careers, set out to find a full-time manager.

Looking for a candidate who combined business experience, a solid public reputation and familiarity with the natural sciences and the University, their first choice was H. L. Russell. In 1930, Russell resigned his deanship to become director of the Foundation he had helped initiate.

Russell's tasks included overseeing the operation of the quality control laboratory which the Foundation had set up to monitor the products of its licensees, executing and administering licensing contracts, developing new business and conferring with the trustees in the management of the Foundation's investment portfolio.

When Russell retired in 1939 he was succeeded by L. D. Barney, business manager, and Ward Ross, general counsel, who were co-administrators until Barney resigned in 1944. Ross then served as managing director until Edwin O. Rosten succeeded him upon his retirement in 1969.

L. D. Barney

Ward Ross

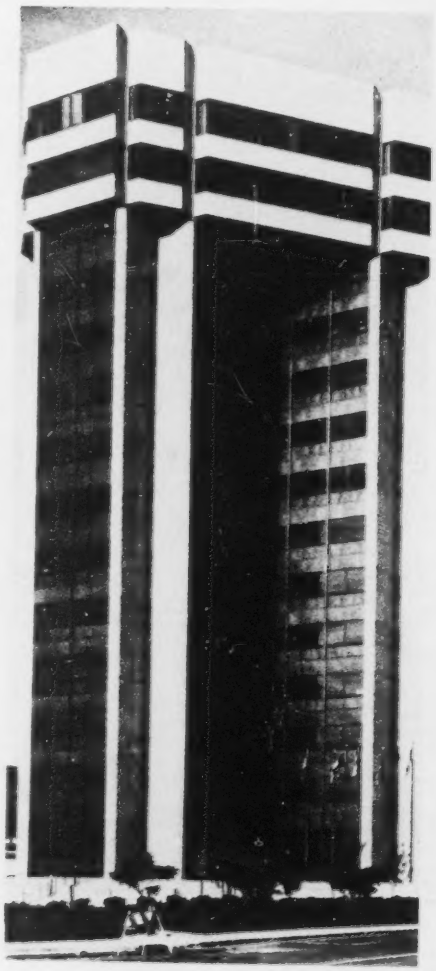
Edwin O. Rosten

On assuming the WARF directorship, Russell moved into the Foundation's first office, room 100 Bascom Hall, which was rented from the University. Shortly afterwards, the administrative staff also took over a small room in the basement of Bascom where for some years L. D. Barney and his staff did their accounting work. These modest quarters housed the small staff until late 1947 when the staff moved to a new building at 506 N. Walnut St. This building, on what was then the extreme western edge of the campus, also housed the Foundation's testing laboratory.

The testing lab had been set up shortly after WARF's vitamin D licensees began marketing irradiated foods, and was intended to ensure quality control of products carrying the WARF seal of approval. The lab had begun operation under the directorship of Dr. Henry Scott on July 1, 1930, in what came to be called the "rickets lab" on the second floor of the Biochemistry Building.

Four years later, the lab had moved across University Avenue to larger, but still hardly palatial, quarters in a barracks-like building which had recently been vacated by the Forest Products Laboratory. The lab remained there until it was moved into the Walnut Street building in 1947.

In 1969, the trustees authorized the construction of a fourteen-floor building one block north of the existing Walnut Street offices. This building, designed by Madison Architect John J. Flad and Associates, soon joined other high rise buildings making up the modern UW skyline, and the WARF administrative staff occupied its thirteenth and part of its fourteenth floors in the early months of 1971. The University uses the remainder as spill-over space for departments which temporarily need extra room for offices.



View from the northeast of the new WARF Building at 614 N. Walnut St.

Fruition: Return on the Intellectual Capital of Ideas

Elmer Severinghaus, Medicine

Edwin B. Fred, Bacteriology

The young Foundation grew rapidly and within a few years was ready to bear its first small crop of funds for the University. As part of the careful effort to keep University and Foundation affairs separate, it was arranged that the money would be parcelled out to researchers by the University's Graduate School research committee.

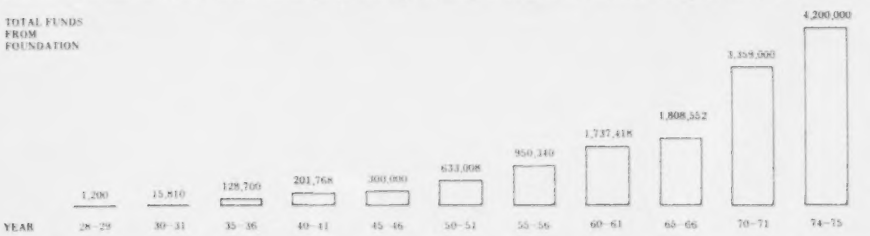
Just three years after the Foundation began, the committee allocated the first WARF grant: $1,200 to W. H. Peterson and E. B. Fred for studies of the action of molds on wood. Since then, research committees—shown here are members of the 1928-29 committee, chaired by Dean Slichter—were to manage an ever-increasing harvest. In its first half-century, WARF's grants to the University have totalled $79,039,217.

Paul Knaplund, History

George Bryan, Botany

Martin Glaeser, Economics

Wisconsin Alumni Research Foundation Summary of Annual Grants to the University of Wisconsin



In 1937, Professor E. B. Fred, marking the tenth anniversary of WARF's first grant to the University, wrote in the Graduate School's "Redbook" report to the trustees: "Perhaps the time has arrived to pause and ask the question: has the research committee distributed these funds so as to fulfill the original objectives of the Foundation?"

In answering his question, Fred pointed to the projects that had been funded: 171 of them the previous year, including Conrad Elvehjem's studies of the antipellagra vitamin, Harry Harlow's early work on monkey behavior and studies by R. Alexander Brink on hybrid corn which were just then helping to revolutionize corn growing in the Midwest.

Confident that the record spoke for itself, the committee included for the first time in the 1937-38 *Redbook* accounts of research projects that had benefitted from WARF support. The pages of this *Redbook* and the 37 issues that have followed dramatically illustrate the value of WARF funds to research at Wisconsin. This value has frequently been far out of proportion to the amount of money involved since the WARF dollars have been there in emergencies, available to fill gaps in government funding, available to back long shots—bright ideas that would later turn into such things as a particle accelerator, satellite instrumentation, or a new drug to fight bone disease.

Above: A distinguished recipient of money made available by WARF in its early years was internationally known Plant Pathologist John C. Walker, shown here at work in the greenhouse. Walker's work on diseases of onions, peas, beets, cucumbers, beans and cabbage formed part of the underpinning of modern truck farming. His yellows, blackleg and clubroot-resistant varieties of cabbage alone were the salvation of a multimillion dollar Wisconsin industry.

Right: "Badger Inbred 16" cabbages in a field at the UW Experimental Farm, Hancock, Wisconsin.

Professor Aldo Leopold, founder of the Department of Wildlife Ecology, came to Wisconsin in 1933 to fill a chair—then called the Chair of Game Management—funded by a special WARF grant. His appointment immediately established the University as a pioneer in ecological studies.

Classical studies of the brain, including pioneering explorations of its control areas, have been the work of Clinton N. Woolsey who came to Wisconsin as Charles Sumner Slichter Research Professor in 1948 to found the Department of Neurophysiology.

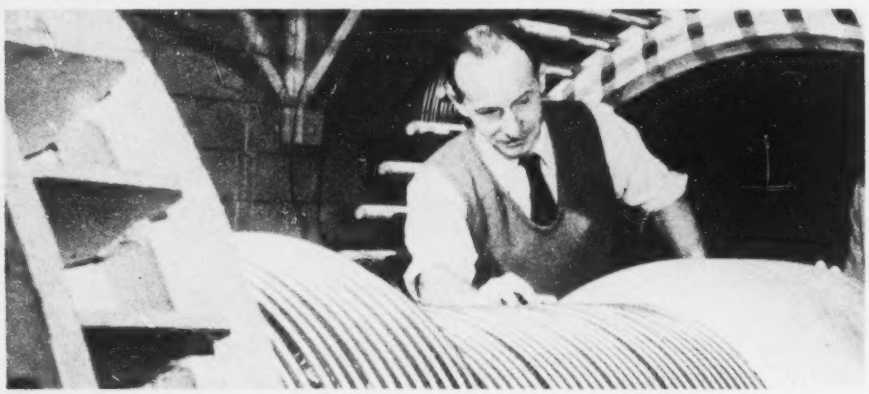
Spending money on genuine research is a kind of gambling, and placing the right bets takes a special kind of skill and inside knowledge. It is one of the strengths of the WARF idea that it delegates full responsibility for allocation of research funds to persons deeply involved in research on campus. Their guide has not been a desire for short-term results or patentable ideas, but only the intellectual curiosity which characterizes a university faculty at its best.

Over the years this has resulted in a long string of "winners," among them men and women who spent their lives opening up areas which 30 or 40 years ago hardly had names, but which have since become departments of the University and branches of knowledge recognized as contributing crucially to man's hopes for the future. This tradition of supporting the curious, as opposed to the obviously practical, continues today.

The 200-year-old mystery of violin tone is yielding to the rigorous approach of Physicist Jack Fry. Fry, who divides his time between subatomic particles and fiddles, has had the support of money made available by WARF for work on both.

With the support of the Foundation, Wisconsin researchers have opened new fields, broadened others-

Some of them remote from human life;



Funds from WARF helped UW scientists contribute to the earliest of the generations of the gargantuan machines needed to study the tiniest particles. Back in the 1930s, at the very dawn of the nuclear age, Physicists Ray Herb, D. B. Parkinson and Donald Kerst had support from the Foundation in building a 2.4 million electron volt Van de-Graff particle accelerator. After some modification in 1938, this "atom smasher" attained a power of 4.5 MeV, a record that stood for nearly 20 years. Herb is shown here inspecting an assembly from a successor of that early accelerator.

...Others close to it.

When Harry Harlow joined the staff of the Psychology Department in 1930, the only place he could study the rhesus monkeys he was interested in was at the Vilas Park Zoo. Dissatisfied, Harlow and his students put up—largely with their own hands—a "monkey lab" of their own on the edge of campus. Since then, WARF funds have helped the Primate Laboratory expand twice. Out of it have come pioneer studies of the behavior of some of man's closest relatives, including Harlow's classic experiments with surrogate monkey mothers. He is shown with one of these here.

In 1960, this outstanding research program attracted a $1,700,000 federal grant to establish on campus one of several National Primate Research Centers, now housed in a new building adjacent to the Primate Laboratory.

Diligently and creatively they have explored Wisconsin's grasslands...

It was prairie that built the rich soil of southern Wisconsin; forests that built the economy of the north. Money made available by WARF supported Botanist John T. Curtis, right, a pioneer student of these great plant communities, in work which led to improved methods of analyzing plant communities, insights into the conditions that influence their development and a classic book—"The Vegetation of Wisconsin"—which summarizes this work.

and the depths of her lakes.

The attentions of University of Wisconsin scientists, beginning with the classic work of Edward Birge and Chancey Juday early in this century, have made Madison's lakes some of the most intensively studied and best understood in the world. Here, in a photo taken about 1950, Professor Arthur Hasler, now director of the Zoology Department's Limnology Laboratory, carries on this work from a wooden rowboat. A recipient of funds made available by the Foundation early in his career, Hasler has since made basic contributions to the understanding of lakes and their inhabitants, including classic studies showing that salmon navigate partly by scent.

The great nebula in the Constellation of Orion, 500 light years away. Its composition has been studied by UW astronomers at the Pine Bluff Observatory.

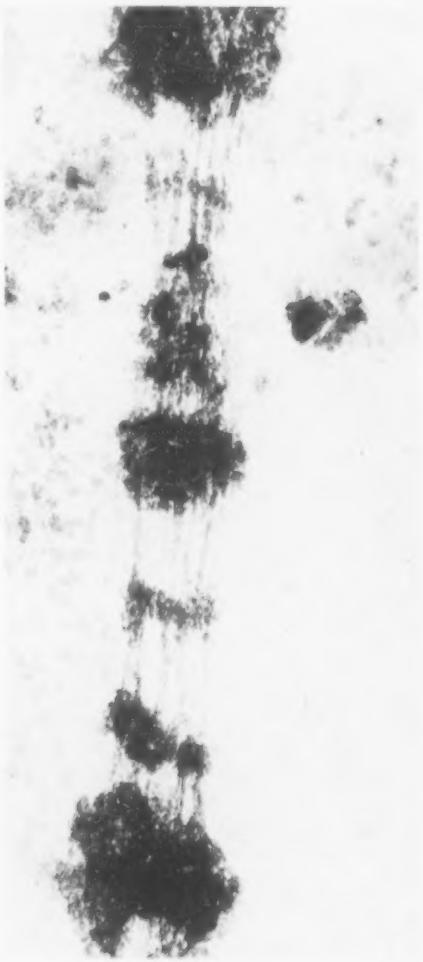
WARF funds have provided tools with which they have explored the universe from its most immense to its minutest aspect.

The hardware that has been purchased with funds from WARF has contributed enormously to making the University the great intellectual toolbox it is today.

In 1958, funds from the Foundation helped erect the Pine Bluff Observatory on a hill 15 miles west of Madison. Using the 36-inch Pine Bluff telescope, UW astronomers have gazed fruitfully at stars, comets, and nebulae, some of the biggest things, and the farthest away, there are to see.

Also gigantic, but built to observe the very tiny, is the High Voltage Electron Microscope (HVEM) which began operation in 1972 in an addition to the Animal Sciences Building partially paid for with money made available by the Foundation. With it, scientists from many departments have ventured in whatever direction their curiosity has led them, studying the composition of materials as well as the most intimate structure of living things.

These impressive tools represent only the extremes on the scale of sizes. In between, WARF funds have paid for a long list of equipment which has made possible many experiments conceived by UW researchers.



Magnified 40,000 times by the HVEM, the sites of genes look like dense snarls in the skein of delicate fibers which make up the chromosome of a fruit fly.
Photo by Hans Ris

Foundation support has had a special value

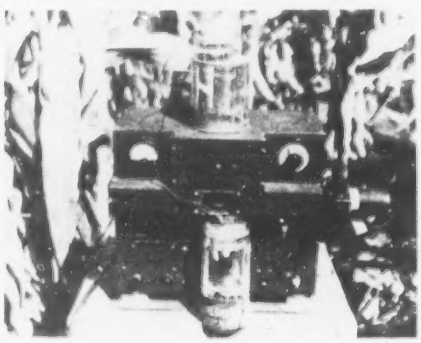
While the Foundation's annual grant makes up only about one percent of all the money the University spends, it has often had a value far out of proportion to its size. This is because WARF dollars are dollars that can be obtained quickly, when and where they are needed, free of the restraints that often limit the value of money from other sources.

Thus, WARF funds have served over the years to fill gaps in state and federal funds and to recruit and retain promising students and distinguished faculty. Money from WARF has helped start many projects which later "graduated" to other sources of funds. And, by serving as a constant reminder that their effort is at least partly self supporting, it has nurtured in members of the faculty a rare sense of the value of their own work.

In getting things started...

A quarter of a century ago WARF dollars were helping to lay the foundations for the Departments of Meteorology and Space Science. One early project was a little dew point device made under the direction of Professor Verner Suomi and shown below measuring the water budget of a cornfield along Willow Drive about 1950.

Ten years later, similar devices designed by Suomi were being sent into space to measure the heat budget of the whole earth. Suomi is shown, left, with the satellite Explorer VII, some of his instrumentation aboard, on the launch pad at Cape Canaveral.



In depression

The depression of the 1930s was the first real test of the Foundation's ability to fill gaps in conventional sources of research funds. Its full force hit the campus in 1932-33 when the legislature simply halved the University's research budget, seriously threatening the quality of the entire program.

In response to urgent pleas from University administrators, the trustees of the Foundation departed from their earlier policy and dipped into capital reserves to provide for 1933-34 an emergency grant of $147,000, more than four times the total for any previous year. This money paid for research leaves for faculty and fellowships for students just completing their doctorates.

As a result, Wisconsin weathered the depression better than many other universities. In 1934, a survey of American institutions placed Wisconsin in the front rank of the nation's universities, ranking it in a tie for first place with the University of California in number of departments providing high quality graduate education.

In addition, the emergency funds had rescued the careers of dozens of young scientists who have since risen to prominence. Some of these have since left; others stayed to build distinguished careers at Wisconsin.

The depression led to another departure from established policy as some WARF dollars during the lean years went for the first time to researchers outside natural science departments. Madeleine Doran and Helen White of English, for example, were among the recipients in the humanities and social sciences who later distinguished themselves as scholars on campus.

Stanford Moore, 1972 recipient of the Nobel Prize in Chemistry. "I was lucky to be one of E.B. Fred's 'WARF boys' in those days when funds from the Steenbock patent were drawing students from all over the United States to the Madison campus."

Elizabeth McCoy, emeritus professor of bacteriology, has made distinguished contributions to a variety of fields including classical work on nitrogen fixation, studies of fermentation and bacterial taxonomy.

Gerard Rohlich became C. W. Cook Professor of Environmental Engineering and a noted student of water pollution and sewage treatment.

Professor Olaf Hougen with instruments in the hydrogeneration pilot plant.

In war

The value of the supply of cash made available to the University by the Foundation was again demonstrated during World War II when WARF funds helped the University gear up in response to the needs of a nation at war.

In chemical engineering, pioneering studies of catalysis under Professor Olaf Hougen led to improved methods of synthesizing artificial rubber and gasoline, products then in crucially short supply.

Botanist John Stauffer and Bacteriologist Kenneth Raper had the help of WARF funds in developing new high-yielding strains of penicillin.

Such work was naturally important to the development of the University as well. Hougen's work, for example, helped the Department of Chemical Engineering achieve the top national ranking among American universities in the years following the war.

After the war, WARF's $2.8 million University Houses project helped the University house a growing faculty as thousands of veterans returned to school. In 1951, this project became one of the largest gifts ever made to the University. Proceeds from its operation have since been used to fund research.

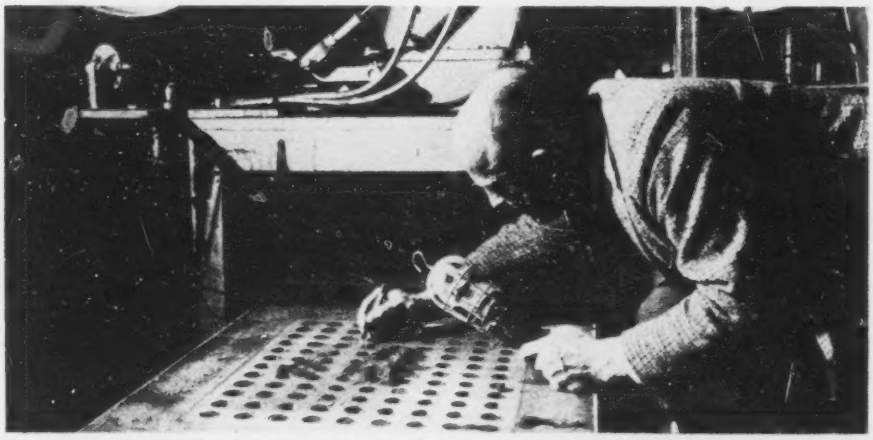
1975 Romnes Fellow Larry L. Cummings, Professor of Business.

and year after year, supporting men at crucial moments

In the summer of 1974, the University announced a program of fellowships using WARF funds to support the research of exceptionally promising junior faculty members. The new program has been named after H. I. Romnes, who joined WARF's board of trustees in 1965 and was its president from 1972 until his death in 1973. It is intended to complement the WARF professorships, awarded for many years to senior faculty members, by helping younger faculty at the time when money is most likely to limit their progress.

Recipients of the fellowship will receive $25,000 each to spend as they consider best for improving the quality and accelerating the progress of their research. The first group, announced last winter, included 11 scholars from departments ranging across the academic spectrum from chemistry and molecular biology to history and modern languages, illustrating the widening scope with which the research committee has allocated WARF funds over the years.

In the future the committee will probably award about five Romnes fellowships annually.



Twenty years ago, Metallurgical and Mining Engineer Richard Heine had WARF money to start work which has led to improved metal-casting methods. Here he checks molds used in research on cast iron.

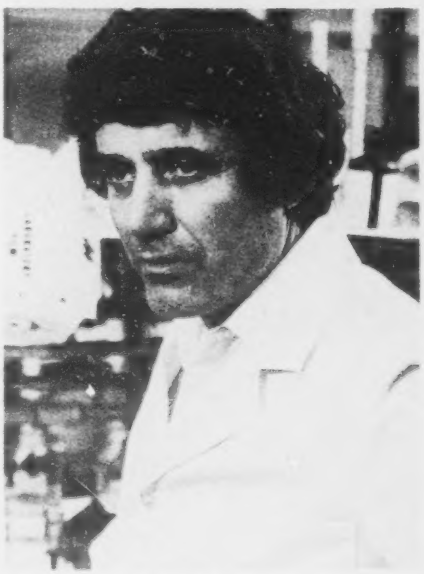
Always with the promise of new generations.

During the Wisconsin Alumni Research Foundation's first half century, the research that led to its creation has continued; under Professor Steenbock until his death in 1967; since then, under one of his last graduate students, Professor Hector DeLuca.

Supported in part by funds from WARF, DeLuca and his colleagues, still working in the suite of laboratories originally occupied by Steenbock on the second floor of Biochemistry, have recently isolated several derivatives of vitamin D, including what they believe may be the active, bone-building, form of the vitamin.

As did Steenbock's pioneering work, these findings represent a basic new insight into human and animal physiology. As did Steenbock's discoveries, they also promise relief from suffering, for they have proven to be the key to the maintenance of healthy bones in persons suffering from certain kidney and liver disorders.

Patents on the vitamin D derivatives are among the newest on WARF's list of "active inventions"; Harry Steenbock's bold and generous idea has borne fruit into its second generation.



Professor Hector DeLuca in his laboratory.

WARF:
50 years

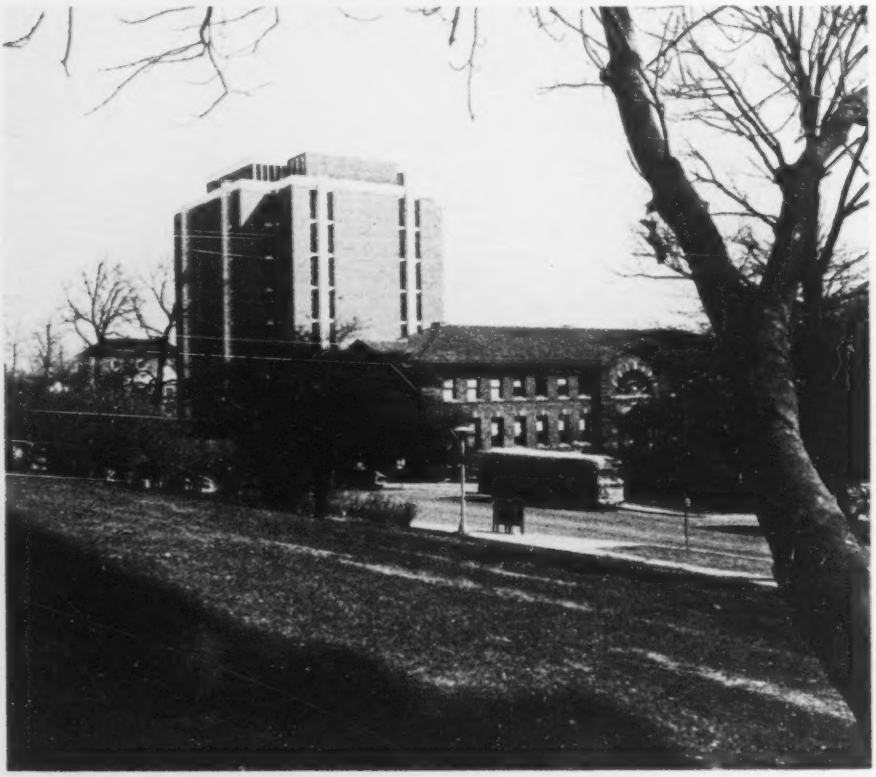
It has helped build a home for the University.

The influence of WARF on the University shows on the campus' skyline as well as in its libraries and laboratories. Funds for several dozen buildings and pieces of major equipment have been provided by the Foundation over the last 30 years.

In many cases, the money from WARF has helped attract matching funds from state, federal or private sources, thus further increasing its value to the University. Overall, building grants from the Foundation have totalled more than $15 million.

The results are now evident for many miles in any direction.

The Molecular Biology and Biophysics Building on Linden Drive, built in 1963 with WARF funds matched by federal and state dollars.



At first, WARF dollars went only to departments in the natural sciences. But, as early as 1928, Dean Slichter was pointing out the need of the social sciences departments for similar support. The spreading of WARF's benefits over the campus began slowly, with assistance going to a number of young scholars in the social sciences and the humanities during the depression. Since about 1960, the research committee has regularly allotted departments in the social sciences and humanities a slice of the WARF pie—more than a quarter of it in 1972-73, for example. A dramatic illustration of how policy has changed since the days when WARF money went exclusively for work in the natural sciences is the Elvehjem Art Center, opened in 1970 to house the University's growing art collection and built partly with WARF funds.

Why it worked at Wisconsin

"First of all, we had a remarkable group of men, descendants, many of them, of the early settlers of Wisconsin.

"We had Steenbock's patent. That was the outcome of devotion and hard work. I remember Harry used to work with those rats constantly and sleep on a cot in the lab. I used to see him buy a bottle of milk and some cheese and crackers and go with nothing else to eat.

"Later, others gave the Foundation very valuable patents. E.B. Hart and Karl Paul Link, for example.

"And we had an unusual policy about patents. At Wisconsin, they say an invention comes out of a man's head and it's his to do with as he wants.

"We had men with the courage to go against the faculty view that a foundation would lead to patent chasing. The record shows it never did. Steenbock wanted to show a man could take out a patent and still be a professor. And he did that.

"We had trustees who knew how to invest money. They kept plowing it back to build up a fund. A lot of people disapproved of that, too. They would have used it right up—killed the goose that laid the golden eggs.

"They kept the Foundation and the University administrations separate. Otherwise it would have turned into, 'You scratch my back and I'll scratch yours.'

"They turned the money over to the research committee, and right away the committee decided not to use it to go after more patents, but only to support basic research. So they watered the roots of the thing, which is quite proper.

"It's all part of the Wisconsin tradition of service. Dean Russell used to send me out around the state to help the farmers with their cheesemaking. And he'd say, 'Don't take a thing from them. Just say the University of Wisconsin sent you.' "

Thoughts of
President Emeritus Edwin B. Fred

President of the University, 1945-1958
Dean of the College of Agriculture, 1942-1945
Dean of the Graduate School, 1934-1943
Co-recipient of the first WARF grant to the University
Professor of Bacteriology and
Member of the faculty since 1913.

400-3J50064-75

THE UNPREDICTABLE PAYOFFS OF BASIC RESEARCH

by Maya Pines

How an Australian aborigine and the curiosity of a geneticist led to the discovery of hepatitis B virus and the cleaning up of blood banks, saving thousands of lives every year.

How this led to the discovery of non-A, non-B hepatitis. How it led to a vaccine against hepatitis B, which may also protect against primary cancer of the liver.

How this may lead to.....

INTRODUCTION

The primary mission of the National Institute of General Medical Sciences (NIGMS), a unit of the National Institutes of Health, is to fund basic research in areas that underlie all medical investigation. Discoveries in cell and molecular biology or genetics, for instance, can be applied to fighting a wide variety of diseases.

The link between basic research and medical advances is not always clear. The case history that follows is designed to illustrate the processes by which basic discoveries are made and become applied to medical problems. It was chosen because the story of hepatitis B—from basic discovery of a suspicious antigen to the ultimate prevention of the disease—is almost complete, and the research involved is still bearing fruit. The events described here are so recent that the scientists who played key roles in them are still active in the field and have contributed their own accounts to this story.

99-177 O - 82 - 17

The symptoms come on rapidly, with fever, chills, fatigue, nausea, and abdominal pain, followed, in many cases, by yellowing of the skin--the classic signs of acute hepatitis, inflammation of the liver.

Hepatitis strikes close to half a million Americans every year. It can be incapacitating; sometimes it is fatal. It has been known since antiquity. Yet until 1963, researchers were greatly frustrated by this disease. There was no cure for it, no prevention, and no way of studying it effectively, since no trace of the viruses which were presumed to cause hepatitis could be found.

As often happens in medicine, the discovery that revolutionized the study of hepatitis came from an entirely unexpected quarter. It did not grow out of "targeted" research on hepatitis, but out of research on more fundamental questions about susceptibility to disease--such questions as: Why do some persons who are exposed to infection succumb to disease, while others, in the same environment, remain in good health? Why do some patients recover rapidly, while others die?

Baruch S. Blumberg, a medical researcher with an interest in human genetics, had been pursuing such basic studies off and on for thirteen years, when in 1963 a drop of blood from an Australian aborigine caught his attention. No other blood sample had ever reacted in the same way to tests he conducted at the National Institutes of Health in Bethesda, Md. Doggedly, he followed this lead through many twists and turns. Although at first it led him to some blind alleys, within three years it brought him to the discovery of the hepatitis B virus--the key to understanding various forms of hepatitis. His discovery opened up many different lines of research and led to an experimental vaccine against hepatitis B, which may yet prove to be the world's first vaccine against a human cancer.

Along the way, Blumberg won a Nobel Prize. As he made clear in his Nobel Prize address in 1976, however, "At the outset we had no set views on where this path might lead...I could not have planned the investigation at its beginning to find the cause of hepatitis B."

The Australia Antigen

Hepatitis was the furthest thing from Blumberg's mind, in fact, when he made the observation which led him on this zigzag trail. He was looking for new "polymorphisms"--genetic variants which are maintained over generations, probably because they give the bearers some selective advantage. About 120 different polymorphisms have been discovered so far, including the well-known ABO blood groups and the Rh factor. But these are only the tip of the iceberg, for it has been estimated that many thousands of polymorphisms exist in humans.

Blumberg reasoned that his best chance of finding such variants in human blood would be among relatively isolated populations, and the more exotic the better. So while at Oxford, England, he studied the blood of Basques and Nigerians, identifying several inherited differences in their sera (the fluid part of their blood). Later on he focused on Eskimos, Indians and Micronesians, and also carried on a long-term study of Australian aborigines together with an Australian colleague, Robert Kirk, who sent him many samples.

"We wanted to see whether inherited differences in the components of blood were related to differences in susceptibility to disease," he explains. "We assumed that, in due course, such a relation would be found, at least for some of the inherited differences, but first we had to find genetic differences between people."

In 1960 Blumberg was working in the geographic medicine and genetics section of the National Institute of Arthritis and Metabolic Diseases at NIH. Together with an associate, Anthony Allison, from the National Institute for Medical Research, London, he decided to give his research a new twist by studying the blood of patients who had received a large number of transfusions. On the theory that blood serum contains many polymorphic proteins, the researchers thought that some of the proteins in the blood which these patients had received would differ from the proteins which they had inherited. And any time that a body is challenged with a foreign substance—a virus, a bacterium, a chemical, or a different kind of blood cell or protein—it responds by manufacturing antibodies against the foreign substance. Such antibodies are extremely specific: they bind precisely to the substance, or antigen, which stimulated their production, making it easier for the body to destroy this antigen. Blumberg and Allison hypothesized that people who had received at least 25 transfusions because of various blood diseases were particularly likely to have developed antibodies against some serum proteins in the donors' blood.

To test this hypothesis, the researchers used a technique of agar gel diffusion which had been developed by Orjan Ouchterlony of the Gothenburg University, Sweden, to detect antigen-antibody binding. They coated a glass slide with agar, a gel, and placed some serum from a patient who had received many transfusions in a well in the center of the slide. The serum diffused slowly through the agar gel. So did samples of six normal persons' sera, which were placed in six surrounding wells. If any components of the normal sera reacted with antibodies from the central sample, a line of white deposit called precipitate would develop where the two diffusing serum samples met.

This actually happened on the fourteenth try, with blood serum from a man in Wisconsin who had had many transfusions to treat his anemia. His serum contained an antibody against certain lipoproteins—compounds containing lipids (fats) and proteins—in the other serum samples, and formed a line of precipitate when exposed to them. This antibody's ability to recognize certain lipoprotein variants rapidly became useful to people doing genetic and, in a few cases, legal studies.

Encouraged by this success, Blumberg continued to look for unusual antibodies in the sera of people who had received large numbers of transfusions, "on the principle that this approach had resulted in one significant discovery and that a further search would lead to other interesting findings," he explained.

Meanwhile, at the NIH Blood Bank, Harvey J. Alter, a hematologist, had been using similar techniques for a different reason: he wanted to find out why certain patients developed fever, chills or rashes after blood transfusions. He thought these people might be suffering from reactions against certain serum proteins in the donated blood. When he learned that Blumberg, too, was looking for antibodies in the blood of patients who had received many transfusions, he went to see him and they decided to collaborate.

Methodically, they tested each serum sample from a frequently transfused patient against panels of sera from normal people of widely varied origins, taken from Blumberg's collection. If a patient's serum showed any reaction at all, it generally reacted with more than half (and up to 90 percent) of the 24 sera in these panels. In 1963, as Blumberg and Alter were studying the blood of a hemophilia patient, a line appeared in reaction to only one of the sera on the panel—and that serum came from an Australian aborigine.

"At that point we had an antigen, but we didn't know what it meant," recalls Alter. "We decided to see whether it existed anywhere else. We knew the hemophilia patient's antibody could detect this antigen, and we began to screen many different populations."

The researchers tested the hemophiliac's serum against thousands of serum samples over several months. Among normal American blood donors, they found, only one in 1,000 had the new antigen, but among patients with leukemia, one in 10 had it, and this was also true for people who had received many blood transfusions because of thalassemia, a hereditary disease which produces severe anemia.

Blumberg, Alter and an associate, Sam Visnich, soon wrote up their observations for the Journal of the American Medical Association in a paper entitled "A 'New' Antigen in Leukemia Sera." They postulated that the "Australia antigen"—named in honor of the aborigine's homeland—was linked to leukemia either as a predisposing factor, or as a result of the disease, or through some virus which might be the cause of leukemia. They considered studying the Australia antigen under an electron microscope to see if it looked like a virus, but did not do so at that time.

Blumberg left NIH to join the Institute for Cancer Research at the Fox Chase Center in Philadelphia, and Alter went to Seattle to do his second year of residency in medicine.

"Had we actually done the electron microscopic studies then, we might have advanced research by at least four years," muses Alter, who is now back at the NIH Blood Bank as chief of the immunology section. "But there were so many lines of research to follow—you couldn't follow them all!" In his opinion, Blumberg deserves credit precisely for "pursuing and pursuing that single finding about the Australia antigen for years, when it could have been dropped at any point."

In Philadelphia, Blumberg came up with the idea that people who had an inherited susceptibility to developing leukemia would also be more likely to have the Australia antigen. Since children with Down's syndrome (mongolism) run a particularly high risk of developing leukemia, he began to test the blood of Down's syndrome patients in a large institution in New Jersey. It turned out that a large proportion—about 30 percent—of these patients did have the Australia antigen. This was a much higher frequency than among other mentally retarded patients in the same institution, and the result seemed to support his hypothesis. A second test of this hypothesis, in a large institution in Pennsylvania, confirmed his results.

However, when Blumberg tested the same hypothesis a third time, among children with Down's syndrome who lived at home with their parents, he did not find any trace of the antigen in their blood. Because of this result, the hypothesis had to be rejected.

Some scientists suggested that the findings of this third study, done on children who lived at home, cancelled out those of the first two studies—and that the net result was zero. But Blumberg viewed all these findings as the raw material for a new hypothesis. Since people who live in institutions are much more likely to become infected by various agents than people who live at home, he hypothesized that (1) the Australia antigen is associated with an infectious agent, and (2) because of a genetic abnormality, people with Down's syndrome are more likely than other mentally retarded patients to become infected with this agent when exposed to it.

Therefore, he began to study some of the factors associated with Down's syndrome which might make these people more susceptible to infection. (As has been learned in recent years, several defects in these persons' immune systems are involved.)

In the midst of these studies, Blumberg and his colleagues at the Institute for Cancer Research, W. Thomas London and Alton I. Sutnick, heard some intriguing news. A 12-year-old boy with Down's syndrome who had had no trace of the Australia antigen in his serum when he was first examined in the state institution suddenly showed signs of this antigen in his blood a few months later. Until then, the presence or absence of Australia antigen had seemed to be a permanent characteristic, much like a genetic trait. Yet there was young James Blair, who apparently had just developed this "new" protein in his blood. Since many proteins are produced in the liver, the researchers did a series of liver chemistry tests on him. To their suprise, they found that James had contracted a form of hepatitis.

At this point it became crucial to test the hypothesis that Au (the Australia antigen) was associated with hepatitis. By the end of 1966, Blumberg had not only found such an association, but had also raised the possibility that Au might be the cause of the disease. Then a technician who had been working on Au in his lab, Barbara Werner, began to feel ill. Being fully aware of the relationship between Au and hepatitis, she tested her own serum for the presence of Au—and found it positive. She subsequently developed hepatitis, and recovered. "This was the first case of viral hepatitis diagnosed by the Au test," Blumberg recalls.

The original paper on hepatitis by Blumberg and his colleagues did not receive wide acceptance. There had been too many erroneous claims about hepatitis viruses by other scientists who thought they had found the cause of the disease and had been proved wrong. A second paper, in which the group extended its findings, was initially rejected for publication on the grounds that it proposed another "candidate virus" for hepatitis, and that there were already many of these. Nevertheless, the association between Au and hepatitis was soon confirmed by a Japanese scientist, Kazuo Okochi, and others, particularly by Alfred Prince of the New York Blood Center.

Unlike Blumberg, Prince is a virologist. He had been interested in hepatitis for about twenty years. While doing his military service in Japan in the early 1960's, he had looked for evidence of a hepatitis virus in the livers of soldiers who had contracted the disease, which is prevalent in the Far East. Although he had actually found some evidence of antigens that might be related to an infectious virus, nobody followed up on in his discovery. It was a time of great discouragement among researchers on hepatitis.

Cleaning Up the Blood Banks

The fact that hepatitis can be contagious had been obvious for centuries. Wars breed epidemics of hepatitis, and so do crowded conditions. Until the middle 1940's, however, doctors could not distinguish between different kinds of hepatitis. At that time, a series of international studies with human volunteers demonstrated that "infectious hepatitis" (now known as hepatitis A) was caused by a virus. The disease was transmitted by contaminated food or water, or by direct person-to-person contact, and had an incubation period of two to six weeks.

Another form of hepatitis was also recognized: "serum hepatitis" (now known as hepatitis B). This, too, was thought to be caused by a virus, but it was believed to be generally noncontagious, except through injection of contaminated blood. For example, large numbers of persons who were inoculated with vaccine against yellow fever developed hepatitis four months after the injections; this was later traced to some human blood serum which had been incorporated in the culture medium during the production of the vaccine. This form of hepatitis had a longer incubation period than the other—two to six months—and was more severe.

Unfortunately, it seemed impossible to isolate--and thus study--the infectious agents which appeared to be responsible for these diseases. Try as they might, researchers could not make these agents grow consistently anywhere--not in laboratory cell cultures, nor in guinea pigs, hens' eggs, hamsters, rabbits, mice, rats, canaries, pigeons, dogs, cats, horses, sheep, and not even in such nonhuman primates as baboons, chimps, marmosets or monkeys. As all these efforts ended in frustration, scientific journals lost interest in the virus research.

Nevertheless, Prince continued to work on hepatitis when he returned to New York. There he met Blumberg, who told him about the Australia antigen. In late 1966, the two men decided to work together to see whether the Australia antigen was part of a virus. The collaboration soon broke up, but Prince started an experiment which was to confirm the association between Au and hepatitis.

Knowing that at least one in ten patients who received blood transfusions would come down with hepatitis, Prince wanted to show that the antigen appeared in their blood during the incubation period of the disease, before they had any symptoms of illness: this is how it happens in most viral diseases. The New York Blood Center, where he worked, was a perfect place to follow up patients who received transfusions.

Under a grant from the National Heart, Lung, and Blood Institute of NIH, Prince began taking blood samples from certain patients at regular, two-week intervals and storing them in a freezer for future use. Finally, in 1968, he heard that one patient whose blood he had collected had developed clear symptoms of hepatitis. Rushing to the freezer, he took out the man's blood samples and tested them. He was thrilled to find that the Australia antigen had appeared in the patient's blood weeks before the illness. This confirmed that Au was involved in the development of hepatitis B.

Meanwhile in Tokyo, Okochi reported preliminary evidence that Au could be transmitted through blood transfusions. Blumberg at once embarked on a controlled study of the effects of blood transfusions from donors whose blood contained the Australia antigen. He wished to determine whether such blood was more likely to transmit hepatitis than blood which did not have the antigen. But in the middle of the experiment, he got word from Okochi that the answer had to be yes. Okochi actually visited Blumberg's lab in Philadelphia in 1969 and showed him the data he had gathered from a similar study in Japan. Blumberg found these data so convincing that he immediately stopped his own study for ethical reasons.

"Before Okochi's data had become available, it was a moral necessity to determine the consequences of transfusing blood containing Australia antigen; and it had to be done in a controlled and convincing manner, since major changes in blood transfusion practice were consequent on the findings," Blumberg explained in his Nobel Prize address. But "as soon as the conclusions of Okochi's well-controlled studies were known to us, it became untenable to administer donor blood containing Australia antigen." The blood was too dangerous.

From then on, would-be donors whose blood was found to contain the antigen were excluded from some of Philadelphia's blood banks, as well as from the NIH Blood Bank. Other blood banks throughout the U.S. rapidly followed suit. This dramatically slashed the rate of post-transfusion hepatitis B among patients.

Until the late 1960's, one out of three patients who received many blood transfusions at NIH and other hospitals developed hepatitis. The risk was particularly high when the blood came from paid donors, many of whom were infected with hepatitis B. As the use of blood from volunteer donors increased and the use of tests for the Australia antigen became universal, millions of persons around the world were spared the risk of contracting hepatitis B. It has been estimated that this produces savings of about half a billion dollars a year in the U.S. alone.

Zeroing In on The Hepatitis Virus

Clearly, blood that harbored the Australia antigen could transmit hepatitis. But was the Australia antigen a virus?

Electron micrographs soon revealed that the sera of people with the Australia antigen contained three different kinds of particles. There were innumerable small, spherical particles, about 20 nanometers (millionths of a millimeter) in diameter. There were sausage-shaped particles of the same diameter, but much longer. And there were some much larger, more complex particles, with a diameter of about 42 nanometers and an inner core of about 26 nanometers, first observed by D. S. Dane of the Middlesex Hospital in London in 1970. These more complex particles, now known as "Dane particles," represent the whole virus and are the only ones that are infectious. Each Dane particle has a surface coat made up of Australia antigen (now termed hepatitis B surface antigen). Its inner core consists of a different protein, hepatitis B core antigen, as well as a molecule of double- and single-stranded DNA. By contrast, the two smaller particles are devoid of DNA and consist entirely of hepatitis B surface antigen.

A person who has been infected with the hepatitis B virus may have an acute illness and recover completely. In this case, surface antigens will appear in the blood for a while but will eventually disappear, to be replaced by antibodies against this antigen—a sign that the person is protected against further in ection with this particular virus.

If, on the other hand, a person who has been infected with the virus fails to produce any antibodies against the surface antigen, continues to harbor surface antigens, and also has a high concentration of antibodies against the core, this means the person has become a chronic "carrier" of hepatitis B.

Although it used to be believed that hepatitis B is not generally contagious, except through blood transfusions, by the late 1960's it had become evident that the virus spreads in many ways. It can be spread by saliva, by semen, and perhaps through insect bites. There have even been reports of its spreading by means of computer cards—presumably, through a cut in the skin. In addition to such "horizontal" transmission, the virus can be transmitted "vertically," from mother to child.

This creates a major public-health problem, for it has been estimated that there are 1 million carriers of hepatitis B in the U.S., and nearly 200 million carriers of hepatitis B around the world. Some of these carriers are infectious. Others (perhaps the majority) are not. It is not yet possible to tell one kind from the other precisely, though a new marker, the "e" antigen, seems to correlate with infectivity.

"We are building a population of hepatitis carriers," declares Maurice Hilleman, a virologist who is senior vice-president of Merck, Sharp & Dohme Research Laboratories and has been involved in the development of several vaccines. The hepatitis B virus is transmitted with particular frequency among male homosexuals; drug abusers who share hypodermic needles; health-care workers and patients in kidney-dialysis clinics; institutionalized mental patients, many of whom are now being integrated into society; the families of Vietnam veterans; and immigrants from Vietnam, Cambodia or Africa. Recently dentists were warned that they should take precautions against infection when filling the teeth of Indochinese refugees who have not been tested for the disease.

People who carry the hepatitis B virus are usually not aware of it. Yet some of them eventually develop chronic active hepatitis. Some of the people with chronic active hepatitis develop cirrhosis of the liver, though most do not. And some of the people with cirrhosis of the liver develop a rapidly fatal cancer—primary cancer of the liver—which, though rare in the U.S., is one of the most common cancers in the world.

Hepatitis B and Cancer

Primary liver cancer attacks five or six times as many men as women. It is particularly prevalent in China, other parts of Asia, and most of Africa. About one million persons die from it every year.

As early as the 1950's, investigators in West Africa had suspected an association between this cancer and hepatitis, but there was no way to prove it—or even to test the hypothesis. The Australia antigen made studies possible. Tests for the presence of this antigen (and therefore of the hepatitis B virus) soon showed that such a link did exist.

Since then, researchers have found many independent lines of evidence which support the hypothesis that persistent infection with hepatitis B virus is necessary for the development of most cases of cancer of the liver. For

example, the cancer occurs most frequently in parts of the world where there are many carriers of hepatitis B. Victims of primary liver cancer have hepatitis B surface antigen and antibodies to the core of the virus in their blood far more frequently than do people who are free of the cancer. Most of the cases of primary liver cancer occur in people who already have cirrhosis of the liver and/or chronic hepatitis. And a prospective study at the Tokyo Women's Medical College, begun in 1973, showed that patients with cirrhosis of the liver who carried hepatitis B surface antigen at the time of their admission to the hospital were four times more likely to develop liver cancer than patients with cirrhosis who did not carry the antigen and whose liver damage had other causes, such as alcoholism.

Other studies in Taiwan and Japan followed up apparently healthy chronic carriers of the hepatitis B virus and compared them with matched groups of people who were not carriers, for periods of up to four years. Of the three cases of primary liver cancer that occurred among 18,000 middle-aged employees of the Japan National Railway in the Tokyo district during this period, all developed in people who were carriers. Of the 34 cases of liver cancer in the more extensive and longer study performed in Taiwan by Palmer Beasley, of the University of Washington, all but one developed among chronic carriers.

In addition, the liver cells of patients with primary liver cancer nearly always show the presence of hepatitis B viral DNA integrated into the cell's chromosomes.

The Hepatitis B Vaccine

One way to protect against hepatitis and liver cancer would be to vaccinate people against hepatitis B. But hepatitis B is so different from most other viruses that a very unorthodox vaccine is required. While other vaccines are made from live or killed viruses that are grown in tissue culture, the hepatitis B virus will not grow in artificial media. Nor can it be tested in the usual experimental animals, since it will not infect them.

In 1969, Irving Millman of the Institute for Cancer Research and Blumberg thought of a novel approach: using the blood of human carriers as a source of antigen. Shortly afterwards, Saul Krugman of the New York University School of Medicine, who had been studying the natural history of hepatitis for fifteen years, made a happy discovery. Krugman had collected hundreds of blood samples from patients at various stages of hepatitis in an institution for the mentally retarded, where exposure to the disease was nearly unavoidable. His earlier research had provided definitive evidence that there were at least two distinct forms of hepatitis. Now he wanted to find out how the hepatitis B virus could be inactivated.

He took some serum that he knew was infectious, diluted it, boiled it one minute, and injected it into new patients at the institution, who had not yet been exposed to hepatitis. This treatment of the virus inactivated it almost completely, and none of the patients showed signs of hepatitis. The happy suprise was that a large proportion of the patients who had received the boiled serum were thereby protected from subsequent infection with hepatitis B. This demonstrated that a vaccine was feasible.

At that point, Merck, Sharp & Dohme became interested in developing a pure and safe vaccine against hepatitis B. Its raw material is blood taken from carriers of the virus—the very same people who are now rejected as donors by regular blood banks. At NIH, Robert H. Purcell and John L. Gerin developed a similar vaccine.

After working on the measles, mumps, rubella, influenza and meningitis vaccines, Maurice Hilleman calls the hepatitis B vaccine "the most technologically complicated vaccine I've ever dealt with." Since only one of the three particles associated with hepatitis B is infectious (the large Dane particle, which contains DNA), the vaccine is made by "harvesting" the smaller particles, which can stimulate the production of antibodies but cannot pass on the infection. As Hilleman points out, however, "one cannot totally separate the particles of surface antigen from the whole virus--and just one molecule of the virus could cause the disease." Therefore, even after the small particles have been purified to the highest possible degree, they must still be treated with chemicals so as to kill any remaining viruses. And even then, each lot must be tested to make sure it is really safe. Fortunately, NIH researchers recently found a way to transmit hepatitis B to chimpanzees, and Merck now tests each new batch of vaccine on four chimpanzees before releasing it.

The first major trials of the hepatitis B vaccine began in 1978, with several groups of volunteers who were at particularly high risk of developing the disease: male homosexuals in six American cities, and patients and staffs of kidney-dialysis centers. The studies were conducted in double-blind fashion, so that neither the scientists nor the volunteers knew who received the vaccine and who received a placebo (an inactive substance). In 1980, Dr. Wolf Szmuness of the New York Blood Center announced that the New York trial had been highly successful: 96% of the 549 young men who were vaccinated showed high levels of antibody to hepatitis B surface antigen, and not one of these men developed the disease during the first 18 months of follow-up. By contrast, 52 of the 534 men who received a placebo came down with hepatitis B during the same time.

Outside of the U.S., the vaccine is being tried in babies as young as three months of age, in the hope that this will prevent them from becoming carriers of hepatitis B.

A possibly more economical and safer form of hepatitis B vaccine may soon be on the way. As a result of recent advances in recombinant-DNA technology, scientists can now insert fragments of hepatitis B virus DNA into bacteria or

yeast cells and make these micro-organisms produce hepatitis B surface antigens. This means that bacterial or yeast factories may be used to manufacture large quantities of hepatitis B vaccine at low cost. This method would be more efficient than a process which begins with infected blood, and would also eliminate any possibility of contamination with infectious particles.

The Discovery of Non-A, Non-B Hepatitis

The discovery of hepatitis B virus made it possible to do research on hepatitis A virus without confusing it with hepatitis B.

In 1973, a decade after Blumberg discovered antigens linked to hepatitis B, Stephen M. Feinstone, who was working in Robert H. Purcell's laboratory at the National Institute of Allergy and Infectious Diseases (NIAID), found viruslike particles in the stool of volunteers who had been experimentally infected with hepatitis A and were in the acute stage of the disease.

In the meantime, there had been major improvements in the tests for hepatitis B. The agar gel diffusion test with which Blumberg had found the Australia antigen was simple and inexpensive, but quite insensitive and slow—it took between 24 and 48 hours to produce an answer. By 1972, rapid tests became available, particularly the radioimmunoassay, which Solomon A. Berson and Rosalyn Yalow had developed as part of their research on peptide hormones at the Bronx Veterans Hospital in New York—and for which she won the Nobel Prize in Medicine in 1977. It proved not only rapid, but 100 to 200 times more sensitive than previous tests.

"Using this assay, we can pick up nearly all carriers of the hepatitis B virus," declares Harvey Alter, of the NIH Blood Bank.

Nevertheless, a number of transfused patients continued to develop hepatitis. Before the radioimmunassay, it seemed likely that the fault lay in the tests, which were not sensitive enough to detect all carriers of hepatitis B. But now it became clear that some other factor must be responsible for at least some of the cases. Some scientists assumed that the guilty virus was hepatitis A; others began to suspect a different cause.

As soon as the NIAID's researchers had identified the hepatitis A virus, they tested 22 patients who had come down with non-B hepatitis after receiving blood transfusions. They were facinated to find that not one case was due to hepatitis A.

"This showed that a fairly large population of patients suffered from hepatitis that was neither A nor B," points out Purcell. He refuses to call this illness "hepatitis C," however, since there is evidence that more than one virus may be responsible for it, and he does not want to repeat the kind of confusion that existed between A and B.

The study of "non-A, non-B hepatitis," as it was dubbed, is now one of the hottest areas of biological research. Three separate groups at NIH are working on it. They realize that non-A, non-B hepatitis presents a serious health hazard, for although its symptoms are generally mild, up to 40 to 50 percent of the persons who contract this illness after a blood transfusion go on to develop chronic hepatitis—far more than the 2 to 4 percent who develop chronic hepatitis after infection with hepatitis B. Eventually, one or more vaccines against non-A, non-B hepatitis may be developed.

Giving "Chance" A Chance

No one can tell where the long and intricate chain of discoveries begun by Baruch Blumberg's interest in a drop of aborigine blood will lead. It has already uncovered three different types of hepatitis virus, cleaned up the world's blood banks (and thus made serious operations infinitely safer), produced a vaccine against hepatitis B which may also be a vaccine against liver cancer, and turned up several clues to how cancer develops. The next links in this chain will appear after yet another burst of work by people with varying interests of their own, and after some puzzling zigzags. This may seem like an erratic process, but it is the way basic research is done.

Much depends on having a critical mass of information in a given field, so that a spark can ignite it. Blumberg's finding of the Australia antigen, for instance, came at just the right time. Thanks to earlier researchers, much information about hepatitis was available, and thousands of samples of sera from hepatitis patients had been collected, making it relatively easy to identify the mysterious antigen. Other basic research had produced the technical tools which Blumberg used, including the agar gel diffusion technique and electron microscopy. Although the scientists who had been doing targeted research on hepatitis were stymied in their search for a hepatitis virus until Blumberg supplied the essential clue, his finding fell on prepared ground.

Much also depends on the quirks, previous experience, curiosity and doggedness of the individual researcher. While it is often said that science advances through a series of lucky accidents, far more than chance or "serendipity" is usually involved in such findings.

The term "serendipity" was coined by Horace Walpole in 1754 after he read a fairy tale about "The Three Princes of Serendip" (Serendip was the ancient name of Ceylon). "As their highnesses traveled," Walpole wrote, "they were always making discoveries, by accident or sagacity, of things which they were not in quest of."

In 1945, the physiologist Walter Cannon popularized the word "serendipity" in an essay on the role of chance or accident in research and discovery.

Since then, it has been interpreted to mean that scientists simply stumble onto their discoveries through no effort of their own—thus leaving out the important part played by what the scientists bring to their chance observations, and what they make of them. As Louis Pasteur said, "Chance favors only the prepared mind."

Blumberg made his chance discovery while pursuing basic research in a field of his choice. Many other discoveries which have provided the key to the prevention or cure of specific diseases have resulted from basic research in unrelated fields. For example, nearly half of the key scientific articles which led to "the top ten clinical advances in cardiovascular-pulmonary medicine and surgery between 1945 and 1975" dealt with topics that were unrelated to either heart or lung disease, according to Julius H. Comroe of the University of California, San Francisco, and Robert D. Dripps, of the University of Pennsylvania.

"Basic reseach is done to find out how things work in nature; it is essentially a search for mechanisms," notes Lewis Thomas, president of the Memorial Sloan-Kettering Cancer Center in New York. When a basic researcher is imaginative enough and deals with a subject in which enough knowledge has been accumulated, he can propel a whole field of science forward by a quantum jump. Then medicine can sometimes move from ineffective and expensive "half-way technologies," as Lewis Thomas calls them, to effective and inexpensive ones. For example, the iron lung, which was used to allow victims of polio to breathe, could be replaced by the polio vaccine, which effectively prevents the disease.

"All of today's medical advances draw on capital from a bank of undifferentiated information produced by basic research--and this bank needs constant replenishment," Thomas declares. "We are still profoundly ignorant about nature. . . We will solve the problems of heart disease, cancer, stroke, arthritis, schizophrenia, senile dementia, and all the rest, if we can just keep learning."

THE THREE TYPES OF VIRAL HEPATITIS KNOWN TO DATE

	Hepatitis A	Hepatitis B	Non-A Non-B Hepatitis
Previous name:	Infectious hepatitis.	Serum hepatitis.	
How spread:	Through contamination of food, water, clothing, toys, eating utensils, etc., by feces.	Via blood transfusion, hypodermic needles, tears, saliva, semen.	Similar to hepatitis B.
Incubation period:	2-6 weeks.	2-6 months.	1-6 months.
Long-term effects:	No lasting liver damage; complete recovery. No cancer risk.	5-10% of patients become carriers, some of whom can transmit hepatitis B to others. 40% of carriers develop chronic liver disease. Hepatitis B has also been linked to primary liver cancer.	40%-50% of patients show evidence of chronic liver disease and are presumably carriers; risk of liver cancer unknown.
Description of virus:	Diameter of 27 nanometers; no outer envelope.	An infectious core, 26 nanometers in diameter, containing DNA and hepatitis B core antigen, surrounded by an envelope of non-infectious hepatitis B surface antigen (formerly known as Australia antigen).	Unknown.
Prevalence of infection:	In the developing nations, nearly everyone is infected with hepatitis A at birth. In the U.S., 80% of the population over the age of 40 carries antibodies to it, evidence of previous exposure to the virus; however, few young adults or children have such antibodies, probably because of improvements in hygiene and public health.	On the average, only 7-10% of the U.S. population has been infected with hepatitis B; fewer than .5% are carriers of the virus. By contrast, 60-80% of the population in Southeast Asia and Africa has been infected with hepatitis B, and 6-10% are carriers of the virus. Certain groups in the U.S., such as male homosexuals or workers in kidney dialysis clinics, have an infection rate of up to 70%.	Unknown.

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P81-16
FOR IMMEDIATE RELEASE
November 16, 1981

(Food and Drug Administration)
Faye Peterson -- (301) 443-3285
(Home) -- (301) 596-9639

STATEMENT

by

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs

I am pleased to announce today the Food and Drug Administration's approval of a new virus vaccine to combat hepatitis B, a debilitating liver disease.

This major advance was brought about by the cooperative effortsof scientists in government, industry and the academic community. This is the first completely new viral vaccine in ten years and the first vaccine ever licensed in the United States that is made directly from human blood.

Hepatitis B is a major public health problem in the United States. There are 200,000 to 300,000 new infections each year, and 100 to 200 victims die of acute hepatitis. Thousands more suffer from degenerative liver disease as a result of hepatitis B infection. Further, there is a reservoir of 400,000 chronically infected carriers, many of whom continue to transmit the disease.

The Centers for Disease Control estimate the cost of hospital treatment alone for hepatitis B, the minimum amount that can be saved by using the vaccine, to be about 4.3 million dollars a week.

The incidence of hepatitis B in some developing countries is much greater than here, and there are up to 200 million hepatitis B carriers worldwide. The new vaccine obviously has the potential for a dramatic effect not only on the health of the people in this country but on those in many other nations as well.

Recent research on the hepatitis B virus has suggested an association with liver cancer. On a worldwide basis, cancer of the liver is the most common form of cancer. It accounts for about 2 percent of all cancers in this country but as much as 20 to 40 percent in some areas such as Africa and Asia. Epidemiological studies show that patients with liver cancer are more likely to have had chronic infection with hepatitis B than the general population. So this vaccine may save people not only from an infectious disease, but from one form of cancer as well.

Hepatitis B used to be called serum hepatitis or post-transfusion hepatitis, because it was thought to be spread only by the transfusion of infected blood, or by unsterile needles used for illicit drug injections, ear piercing or tatooing. But the virus is now known to also be present in carriers' tears, saliva and semen and to be spread by intimate contact, including sexual activity. Thus, persons at high risk to the disease include those who handle equipment in blood banks or kidney dialysis units, surgeons, dentists and others who come into contact with chronically infected individuals. Also at high risk are drug addicts and people with a very large number of sexual contacts such as some male homosexuals.

This vaccine, though very important, is not for general, population-wide use. I want to make clear that not everyone needs to take this vaccine. Indeed, it will be recommended initially only for people at high risk of acquiring the disease, such as health care workers, institutionalized mentally handicapped patients, laboratory workers, hemodialysis staff workers and patients, contacts of certain carriers, some military personnel and persons with numerous sex contacts. Because of the very lengthy production time, the vaccine will not be available for broad distribution until mid-1982.

The discovery and development of this vaccine resulted from many years of hard work. The first major breakthrough in hepatitis B research came in 1965 when Dr. Baruch S. Blumberg of the Institute for Cancer Research, Philadelphia, and Dr. Harvey Alter of the NIH Clinical Center Blood Bank discovered evidence of the presence of the virus in the blood of an Australian aborigine.

99-177 O - 82 - 18

Subsequent studies revealed that this particle was part of the outer coat of the human hepatitis B virus. Tests ultimately led to a method of detecting hepatitis B infection and hepatitis B carriers.

The first studies showing that viral antigen in human blood might, itself, be used as a vaccine were conducted in 1971 by Dr. Saul Krugman of New York University, who demonstrated that boiled serum containing hepatitis particles provided protective immunity in recipients.

Since the virus could not be grown in the laboratory, Dr. Blumberg suggested that it might be possible to purify the particles found in the blood of carriers to mass-produce a vaccine. Spurred by Dr. Blumberg's hypothesis, scientists from the National Institutes of Health, including Drs. Robert Purcell, John Gerin, and Franklin J. Tyeryar of the National Institute of Allergy and Infectious Diseases, mounted studies to determine the feasibility of preparing a purified and killed, or noninfectious, vaccine.

A parallel and major challenge to vaccine development was to develop animal models and tests that could be used to evaluate the safety and effectiveness of the vaccine. Scientists making major contributions in this area include Dr. James Maynard, CDC, and Drs. Lewellys Barker (currently of the American Red Cross), Robert Gerety, Edward Tabor and Linda Smallwood of FDA's Bureau of Biologics. Working collaboratively, they found in the early 1970's that chimpanzees were susceptible to -- or could "catch" -- hepatitis B infection. This knowledge led to the use of these animals to test the safety and effectiveness of the experimental vaccine.

Also pioneering in the development of hepatitis B vaccine were scientists from Merck Sharp & Dohme of West Point, Pa. In a program that began in 1968, they undertook development of a vaccine, including a method by which large quantities of it could be mass-produced, and they carried out safety and efficacy trials in chimpanzees and in humans. Drs. Maurice R. Hilleman, William J. McAleer, Eugene B. Buynak and Arlene A. McLean at Merck are responsible for this aspect of the vaccine's development.

A number of the people I mentioned are here today and will be available to answer questions about their research.

Hepatitis B vaccine is the first ever to be manufactured directly from human blood. Other vaccines such as polio and measles are produced from viruses grown in tissue cells in the laboratory.

Production and testing of the hepatitis B vaccine takes about 65 weeks -- longer than for any vaccine currently manufactured -- because of the unique and complex production process and the necessary time for adequate testing. This process begins with the collection of blood plasma from chronic hepatitis carriers in specially FDA-licensed blood donor centers in major metropolitan areas across the country. The non-infectious hepatitis B particles are separated from the blood and purified by laboratory methods. The preparation is then treated with chemicals and enzymes to destroy any live virus.

Merck has designed and constructed a special facility for manufacturing the vaccine. The building consists of a series of sterile laboratories in which each of the stages of vaccine production is carried out.

Clinical trials of the hepatitis B vaccine began in 1975 in a small number of Merck executives. Subsequent trials in more than 3,000 children and adults showed the vaccine to be safe and a good stimulator of antibodies. A total of more than 5,000 persons has received the vaccine in clinical studies.

Studies by Drs. Wolf Szmuness and Clad Stevens of the New York Blood Center in 1,083 men recruited from the homosexual community in New York City showed that three 40-microgram doses of the vaccine given during a six-month period gave an impressive degree of protection: 96% of the volunteers developed protection.

More recently, data from a study conducted by Drs. Maynard and Donald Francis of the Centers for Disease Control demonstrated that only 20 micrograms of vaccine given in 3 doses is actually necessary to provide protection. This trial involved 1,400 high-risk individuals -- male homosexuals -- in five cities, Chicago, Los Angeles, San Francisco, St. Louis and Denver.

The dose and regimen used in this study are the ones that will be approved. The vaccine is given in three 20-microgram doses, with the second dose given one month after the first, and the third, a booster shot, given six months after the first.

I want to commend the individuals who participated in the collaborative research effort -- scientists from government and industry and the volunteers who participated in the trials -- for their roles in developing this vaccine. The American public is greatly in their debt.

By licensing this vaccine we are taking a major step in health care. If we can break the chain of disease transmission through vaccination of the high-risk groups, we may be able to eliminate or greatly reduce the spread of this major, costly disease.

####

NIH MINUTES OF SITE VISIT TO MASSACHUSETTS GENERAL HOSPITAL (MGH)

Site Visit Discussion Subject
Effects on NIH Sponsored Agreement of the MGH
Contract with Hoechst AG, a German Company

On December 15, 1981, a meeting was held to discuss the effects of the Hoechst (pronounced Hurkst') agreement. Representing the Hospital were the following:

Dr. Ronald Lamont-Havers, Director for Research Administration
Mr. Ernest Haddad, MGH General Counsel
Mr. Joseph McCue, Director of Fiscal Affairs, MGH
Mr. Michael Broad, MGH Staff Counsel
Mr. Dave Donaldson, Atty., Ropes and Gray
Mr. Marvin Guthrie, former Director of Office of Technology Administration
Mr. Larry Martin, Associate General Director, MGH
Mr. Ted Chase, Member, MGH Corporation
Dr. Howard Goodman, Chief of the Laboratory of Molecular Biology, MGH
Ms. Sheila Anzuoni, Executive Secretary

Government participants included the following:

Dr. William Raub, Director of NIH Office of Extramural Research and Training
Mr. Hank Kirschenmann, Director, DHHS Division of Procurement, Assistance and Logistics
Dr. Charles Lowe, Associate Director for Medical Applications of Research, NIH
Mr. Leroy Randall, Atty., DHHS Patents Branch
Mr. Richard Riseberg, Chief, NIH Branch of Office of General Counsel
Mr. Ron Gardner, GAO Liaison, Division of Management Survey and Review, NIH
Mr. Walter Boland, Director, Division of Cost Allocation, Region I, DHHS
Mr. Phillip Simard, Senior Negotiation Specialist, Division of Cost Allocation, Region I, DHHS
Mr. Richard J. Powers, Chief, Financial Advisory Services Branch, NIH

After introductions, Dr. Lamont-Havers asked Dr. Raub to indicate what the NIH contingent hoped to achieve or cover during the meeting.

Dr. Raub stated that NIH would want to discuss interactions of MGH and Hoechst, and MGH and NIH in relation to MGH's fulfillment of its obligations under the Hoechst agreement. However, he made it clear that we did not want to discuss or focus on

the specific provisions of the Hoechst agreement. Dr. Raub expressed a hope that the discussions would put both MGH and NIH in a better position to respond to the GAO letter report and any follow-up fact finding or info gathering that GAO engages in. After indicating that MGH had not been able to obtain a copy of a final draft of OMB Bulletin 81-22, Dr. Lamont-Havers began walking the group through background materials that he had prepared for the NIH site visit.

Dr. Lamont-Havers provided a schedule of direct research expenditures by MGH for fiscal years 1965 through 1980. He noted that while the $1,243,000 of industry direct support was only 4% of MGH direct support in 1980 (i.e., $28,877,000), the amount of industry support had increased substantially since 1965 and the Hoechst and Dynex agreements would increase the percentage of industry support to 14% (of total expenditures) in 1982.

Dr. Lamont-Havers then traced the MGH organizational framework as it relates to research and patent activities. As an introduction to the subject, he stated that in the early 1970's it became obvious that Federal funding had become grossly unstable and that more efforts would have to be expended to seek out alternative sources of support for research. Accordingly, the MGH Scientific Advisory Committee immediately began consideration of issues relating to patent policy - efforts which resulted in the formation of a Patent Committee and development of a formal patent policy. The Patent Committee members found out quickly that the efficient resolution of patent issues required the services of a patent attorney and Mr. Guthrie was hired to fill that need. Shortly after his hiring, Mr. Guthrie was appointed Director of the newly formed Office of Technology Administration. Dr. Lamont-Havers concluded the organizational overview by noting that both the Patent Committee and the Scientific Advisory Committee report directly to the Board of Trustees, with the Committee on Research (COR) reporting to the Board. He pointed out that the

Office of Technology Administration functions as an administrative arm of the Patent Committee.

Dr. Lamont-Havers referred briefly to the background materials describing the purpose of the Office of Technology Administration and noted that it was currently undergoing a major restaffing - an effort that included finding a replacement for a very highly regarded Mr. Guthrie.

Dr. Lamont-Havers then referred to the documents that had been developed to assure the proper handling of inventions that resulted from either clinical or research activities. The documents presented to the group were (1) a copy of a Participation Agreement between MGH and its employees specifying the employees' obligations in respect to discoveries or inventions, (2) a copy of formal Patent Policies and Procedures (issued 2/77), (3) a copy of MGH's Policy on the extent to which MGH investigators could do outside consulting drawing on expertise developed from work performed as an MGH employee, and (4) a copy of MGH's Invention Disclosure Statement.

Dr. Lamont-Havers then moved to a discussion of the efforts that had been expended to develop "Academic Goals and Principles for MGH - Industrial Relations." He presented a copy of a draft statement on such "Academic Goals" prepared by an "Advisory Committee on Industrial Relations." (The draft statement is apparently intended to notify industrial sponsors like Hoechst that MGH will not permit any sponsors to place restrictions on academic freedom of investigators.)

The last document presented to the group was a draft copy of OMB Bulletin 81-22 (Patents - Small Firms and Nonprofit Organizations). Everyone agreed that the conclusions reached in the meeting might be affected by changes to the draft Bulletin that were to be issued in January 1982.

Dr. Lamont-Havers then asked Mr. Guthrie to discuss the listing of inventions developed by MGH since 1976. (For obvious reasons, the participants were asked to return their copies of the listing to Mr. Guthrie at the end of the discussion.) Mr. Guthrie noted that there were 30 inventions in 1980 and 27 in 1981 (through November). (Apparently, the primary reason for discussing the listing was to show the attention that was given to determining the extent of Federal support in the development of the invention. Dr. Lowe raised a question about Invention 01-79 and the Secrecy Agreement with Medi-Tech, referred to in providing the particulars of the invention. Mr. Guthrie explained that the Secrecy Agreement was not as sinister as it sounded - that in fact it was nothing more than an agreement to keep information regarding the invention confidential. Mr. Guthrie then described the efforts that MGH had been expending (since 1976) to educate Department Heads (Heads of Services) in respect to what in fact was an invention and what might be patentable within a particular service. Since 1976, the Office of Technology Administration staff (principally Mr. Guthrie) has periodically met in laboratory conference settings with Department Heads and investigators/clinicians reporting to them to discuss invention/patent issues, and particularly to discuss the issue that has caused the most problems, that is, the desire to publish prior to determinations as to whether the research produced a patentable invention. Mr. Guthrie also mentioned that he often attended meetings of the Subcommittee on Review of Research Proposals to determine if anything was being worked on that might result in an invention.

Dr. Raub asked Mr. Guthrie if better review by NIH of grant progress reports might assist in identifying possible inventions. Mr. Guthrie did not like the idea of NIH looking at progress reports from that perspective. He stated that MGH might have to hire three more people to answer questions that might arise from such reviews.

Hank Kirschenmann asked what controls were in effect to assure that invention disclosure statements properly cited Federal support for the research that produced the invention. Dr. Lamont-Havers replied that there is a record kept of all support provided to an individual investigator and this record is referred to in reviewing disclosure statements. Mr. Guthrie added that if the investigator did not check the Federal support line in preparing the disclosure form, he personally would review the investigator's sources of support, the progress reports submitted to Federal agencies, and the support for materials used and technicians assisting in the invention-producing research. He stated that when there is doubt about the extent of Federal support, he forms a committee of the investigator's peers to consider the question of whether the work was supported by Federal funds.

Mr. Randall asked about an invention resulting from research that was supported by industrial sponsors where the investigator collaborated with another investigator that was supported by Federal funds. Mr. Guthrie responded by saying that if such collaboration had taken place, MGH would conclude that the research producing the invention was indirectly supported by Federal funds.

Dr. Raub asked about situations where there was a question concerning whether Government funding was contemporaneous to the development of a concept or idea leading to an invention or whether the idea was developed prior to Federal funding. Mr. Guthrie indicated that such questions would be resolved through discussions with the affected Federal Agency.

Dr. Lowe indicated that the agenda he had prepared prior to the meeting focused on MGH/Federal Patent Management and that a question underlying his agenda topics was "How does MGH handle inventions resulting from research where there has been a commingling of supporting funds?" Mr. Martin asked Dr. Lowe what was meant by a "commingling of funds." Dr. Lowe referred to a situation where research

projects would be supported by multiple sources. Dr. Lamont-Havers said that collaboration of scientists could cause commingling of funds but there was, as Mr. Guthrie indicated previously, a MGH administrative apparatus (committee management) that operated to determine if there was in fact collaboration that resulted in an invention. Dr. Raub asked about the amount of discussion that MGH had had with Hoechst concerning the topic of collaboration. Mr. Donaldson responded that there was a great deal of discussion on the subject of collaboration, and as a result, the contract includes a provision that gives Hoechst the right to fund all of the research in the Department of Molecular Biology (DMB)--effectively a right of first refusal to support all DMB research projects. If Hoechst elects not to fund a research project proposed by the Department, DMB may pursue funding from other prospective sponsors. These other funding sources will be able to obtain whatever rights they would normally require as a condition of their research support. Also, Mr. Donaldson stated that DMB investigators remain free to collaborate with other researchers. If, however, MGH arranges such collaboration, the contract with Hoechst requires MGH to consider Hoechst's interest in obtaining exclusive worldwide licenses to patents arising from Hoechst-supported research projects. Nevertheless, it is recognized that where collaboration takes place, the rights of the various funding sources will attach and govern the disposition of any potential invention arising from such collaboration.

Dr. Lowe asked if multiple funding sources problems could be solved by giving Hoechst right of first refusal to license. Dr. Lamont-Havers responded by saying that its other industrial sponsors would not want Hoechst to have right of first refusal to license.

Dick Riseberg asked whether MGH had had problems with projects supported by two or more industrial sponsors. Mr. Guthrie stated that contracts with industry are very

specific as to what research is being supported, so problems of overlap are generally avoided.

Leroy Randall asked for some specific data relative to the amount of research being performed and the number of investigators employed to do the research. Dr. Lamont-Havers indicated that research performed by 350 investigators in 1981 resulted in expenditures of $37 million. He estimated that of the 350 investigators, 200 were M.D.'s and 150 were Ph.D's. He also estimated that the $37 million was expended on 100 NIH projects and 70 non-NIH projects. He added that there were approximately 2000 employees engaged in research and that inventions in 1981 had come out of both research and clinical activities.

Dr. Lowe asked for a reaction to the issue raised in Topic No. 4 to his agenda for the meeting; that is, the requirement (OMB 81-22) that "exclusive license to practice patents in USA be awarded to industries manufacturing substantially in the USA." Mr. Donaldson stated that MGH would do what it was required to do by law.

Leroy Randall asked if there were collaborative research funded by Hoechst and NIH, and the required nonexclusive license was insufficient to cause Hoechst to want to manufacture, would MGH be bound by the law regarding the Government's march-in rights? Messrs. Donaldson and Guthrie both replied to this question with essentially the same answer: "MGH/Hoechst will comply with the law." Specifically, "if the Government exercises its march-in rights to give another party an exclusive license and thereby promote utilization, MGH/Hoechst will not oppose a Federal direction to grant a license(s) to responsible applicants." Mr. Donaldson added that the "Due Diligence" clause (G.3.D.) in contract permits MGH to withdraw an exclusive license if Hoechst does not begin actual commercial development of an invention "as soon as practicable."

Dr. Lamont-Havers asked what NIH review mechanism is extant for determining when march-in rights are exercised. Dr. Lowe indicated that institutions are asked to define adequate performance by licensees and NIH monitors that adequate performance. On a related subject, Mr. Guthrie asked if NIH is going to require that nonexclusive licenses be revoked by MGH if MGH decides that invention development is not in the public good. Dr. Lowe replied that NIH will not burden MGH implicitly or explicitly with local march-in requirements.

Hank Kirschenmann asked if Hoechst will accept MGH's determination that there is indeed a Government interest in an invention. Mr. Donaldson replied that Hoechst is contractually obligated to accept decisions of the Scientific Advisory Committee. Larry Martin added that the contract provides that Hoechst may go to Federal Court to contest "a determination of contamination." Dr. Lowe asked what would happen if NIH advised that there is a Federal interest in an invention. Larry Martin responded that MGH would discuss NIH's observations/contentions and will concur if mutual review supports NIH's opinion. Dick Riseberg asked "If a significant amount of money were riding on a no-Federal involvement decision, what would happen?" Mr. Donaldson indicated that the Hoechst contract acknowledges that in case of dispute, Federal law will prevail. Mr. Guthrie reaffirmed Mr. Donaldson's position.

Dr. Lowe asked how MGH would decide whether to report inventions to Hoechst or to NIH. Mr. Guthrie replied that the Office of Technology Administration would decide based on review of Invention Disclosure Statements. Dr. Lamont-Havers added that MGH invention disclosure review procedures even extended to "intellectual property." On that subject, Mr. Guthrie indicated that MGH had obtained all records of Dr. Goodman's support from the University of California (UC) system and will decide at invention disclosure time whether there was practical application at MGH of an idea originating when Dr. Goodman was working on NIH-supported projects at UC. If such a determination is made, MGH will report the invention to the University of California and NIH.

Moving to another subject, Leroy Randall opined that where there is an invention disclosed and both Federal and Hoechst funds are involved, the report to NIH should be submitted within the same thirty (30) day time frame that related reports are required by contract to go to Hoechst. Mr. Donaldson agreed that this would be done, even if the time period set by the final OMB Circular was longer.

Referring to Topic No. 2 (Reporting-Intention to Patent) in his meeting agenda, Dr. Lowe asked how MGH would assure that inventions arising out of previously supported research will be reported to NIH. Mr. Donaldson replied that the Office of Technology Administration would decide on the mechanics.

Dick Riseberg indicated that in circumstances where Federal funds contributed to an invention disclosure, it appears Hoechst will get a nonexclusive license until NIH marches in and decides whether license should be exclusive for another laboratory. Mr. Donaldson stated that MGH will comply with the law.

Dr. Lowe asked if payments by Hoechst will be offset by all royalties where licenses have been granted to firms other than Hoechst. Mr. Donaldson replied that only the royalties paid by Hoechst will be offset.

Referring to Topic No. 7 in his agenda, Dr. Lowe pointed out (per OMB Bulletin 81-22) that if MGH subcontracts, the right to patent does not apply to a subcontractor unless it is a small business or nonprofit institution. However, he noted that notwithstanding this provision in 81-22, NIH Patent Policy requires that the right to patent remain with prime contractor. Mr. Donaldson stated MGH would comply with NIH policy.

Dr. Lowe indicated that MGH should be aware of NIH's requirements for data when reporting on inventions. He stated that where there are joint licenses, the dollar value of the licensees' capital commitments to the development of the invention

must be furnished, and, in addition, information re royalty requirements must be supplied. Mr. Donaldson indicated that Hoechst/MGH will meet all reporting requirements.

The meeting adjourned for lunch.

After lunch, Dr. Lamont-Havers asked Dr. Goodman to explain why it was decided to enter into the contractual arrangement with Hoechst. Dr. Goodman indicated that the contract enabled him to pursue research initiatives that he was not able to pursue in San Francisco. He stated that the long term nature of the contract facilitates recruitment of quality scientists and reduces the amount of time that he and his staff will have to spend on "grantsmanship." He mentioned that while he was at the University of California, he had to spend two months of every year in efforts to assure continuation of support from five different Federal agencies.

Dr. Lowe asked Dr. Goodman if it was permissible for DMB scientists to request research funds from the Government. Dr. Goodman replied that he expected that Federal support will be solicited and that we should be assured that MGH will comply with all laws and policies regarding separate accounting. He added, however, that if the MGH/Hoechst combine permits a significant amount of Federally-supported research to go on in DMB, it will be acknowledging that its interest in future patentable inventions may be limited.

Mr. Riseberg asked Dr. Goodman about the extent to which he will collaborate with scientists both within and outside MGH. Dr. Goodman replied that he did not intend to change his communication exchange practices.

Mr. Randall asked what Dr. Goodman's publication policy would be if NIH supports an area in basic research which appears promising, so that it is transferred

to Hoeshst for applied research that results in an invention. Dr. Goodman stated that publication from the basic research area would never be held up for more than 30 days, so that the NIH supported research results would be made promptly available to the entire scientific community.

Dr. Lowe asked about a situation where DMB employs a staff of forty scientists and one of those scientists brings to DMB a research project from another institution that was previously sponsored by Federal funds. Mr. Guthrie stated that all inventions will be screened to determine whether there was Federal support for the conception leading to the invention prior to execution of the Hoechst agreement.

At this point, Dr. Lamont-Havers asked Mr. McCue, Director of Fiscal Affairs, to profile the accounting system that will be used to account for Hoechst expenditures. Mr. McCue indicated that a full-time administrator will be responsible for all budgeting and accounting for expenditures under the Hoechst contract. He stated that, of course, Dr. Goodman will have the primary input for the development of budgets that are to be submitted to Hoechst at the beginning of each quarter. He added that the quarterly expenditure report (called for in the contract) will be prepared primarily by the contract administrator. He also noted that two separate accounts will be maintained - one for capital addition activities and one for operating expenditures. Mr. McCue indicated that indirect cost funding under the Hoechst contract will be determined through the use of indirect cost rates established for use in funding Federal awards (i.e., 51.7% of salaries and wages). Hank Kirschenmann asked if the Hospital had been able to determine whether any Federal funding had been used to construct the facility (Jackson Tower) in which DMB will be housed initially. Mr. Martin replied that approximately $2.25 million (approximately 10% of the overall construction cost) had been provided in 1965 for the construction of the Jackson Tower by the NIH Division of Research Facilities

Resources (DRFR). Hank opined that he felt that those grants provided that the facilities constructed by DRFR funds had a requirement for "continued use for the intended purpose" for a period of twelve years after completion of construction. If that were the case, he stated, it's likely the twelve year period would have expired and the question of use of research facilities by personnel funded exclusively by non-Federal sources would be resolved. Dr. Raub indicated that the NIH team would look into that question upon return to Bethesda.

Dr. Lowe completed the questioning of MGH representatives by asking about MGH's policy for payment of royalties to inventors. Dr. Goodman replied that MGH would comply with all NIH and/or Federal rules in this area.

Dr. Raub ended the meeting by indicating that we were appreciative of MGH's willingness to meet on short notice to discuss a subject that had received a great deal of public attention, and that we were pleased with the unreserved and direct answers that we received to some very sensitive and complex questions. Both sides agreed that summaries of the meeting discussions would be exchanged in order to assure that there was mutual agreement on the essence of MGH's and the Government's position on all of the important issues that arose during the meeting.